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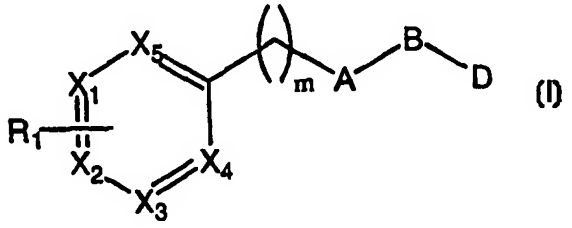
(54) Title: NOVEL PIPERIDINES AND PIPERAZINES AS PLATELET AGGREGATION INHIBITORS

(57) Abstract

Compounds of formula (I) and their salts, solvates and prodrugs are platelet aggregation inhibitors and are useful for the treatment or prevention of thromboembolic disorders. Pharmaceutical compositions including these compounds and processes for their preparation are also provided.



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Novel piperidines and piperazines as platelet aggregation inhibitors.

Field of the invention.

The present invention relates to a new series of piperidines and piperazines which are platelet aggregation inhibitors. The invention also relates to processes for preparing these compounds, to pharmaceutical compositions containing them and to their use for the treatment of disorders in which platelet aggregation is involved.

Background of the invention.

Platelet function plays an essential role in the maintenance of blood hemostasis but also in the pathogenesis of a broad range of cardiovascular and cerebrovascular disorders, including unstable angina, myocardial infarction, atherosclerosis, thromboembolism, stroke, restenosis following angioplasty, etc.

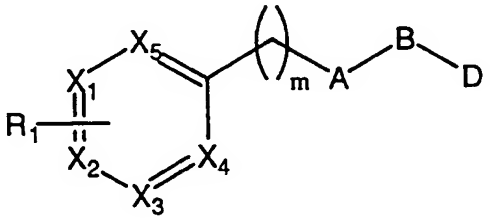
The hemostatic plug consists essentially of a mass of platelet aggregates and a net of an insoluble protein known as fibrin. In order to be able to aggregate, platelets must previously become activated and this activation process involves, as a last step, the exposure of certain cell adhesion molecules on the external surface of the platelet membrane. These molecules are glycoproteins (GP IIb/IIIa) belonging to the integrin family and they act mainly as receptors for fibrinogen although they also show affinity for other adhesion molecules such as fibronectin, vitronectin and von Willebrand factor. Fibrinogen (the soluble precusor of fibrin) is able to bind to two molecules of GP IIb/IIIa on adjacent platelets, leading to the formation of the platelet thrombus.

GP IIb/IIIa, like many other integrins, exhibits high affinity for the tripeptide sequence Arg-Gly-Asp, which is present in many ligands. Several peptidic compounds based on this sequence have been reported which block the binding of fibrinogen to its receptor, thus inhibiting platelet aggregation. However, their therapeutic utility has been severely limited by their low oral bioavailability and metabolic stability. Nonpeptide antagonists of the fibrinogen receptor have also been reported. The present invention discloses new and potent, orally-active nonpeptide inhibitors of platelet aggregation. It is

believed that these compounds act as antagonists of the fibrinogen (GP IIb/IIIa) receptor.

Description of the invention.

The present invention provides novel compounds of general formula I:

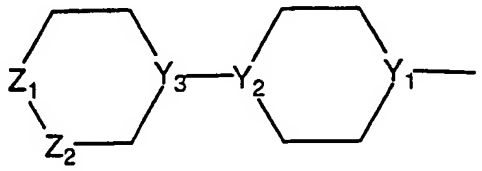


I

wherein:

one of X_1 or X_2 represents C substituted with the group R_1 and the other represents CR_2 or N, and the remaining groups X_3, X_4 and X_5 independently represent CR_2 or N, with the proviso that the ring cannot contain more than two N atoms;

R_1 represents a group of formula:



wherein the terminal ring can be optionally substituted with one or more C_{1-4} alkyl groups;

R_2 independently represent hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl, heteroarylC_{0-4} alkyl, cyano, nitro, $R_3R_4NC_{0-4}$ alkyl, $R_5SO_2NR_3C_{0-4}$ alkyl, $R_5CONR_3C_{0-4}$ alkyl, $R_5OCONR_3C_{0-4}$ alkyl, $R_3R_4NCONR_3C_{0-4}$ alkyl, $R_5SO_qC_{0-4}$ alkyl, $R_3R_4NSO_2C_{0-4}$ alkyl, $R_3R_4NCOC_{0-4}$ alkyl, R_5COC_{0-4} alkyl, $HOOCC_{0-4}$ alkyl, R_5OOCC_{0-4} alkyl, hydroxyC_{0-4} alkyl or R_5OC_{0-4} alkyl;

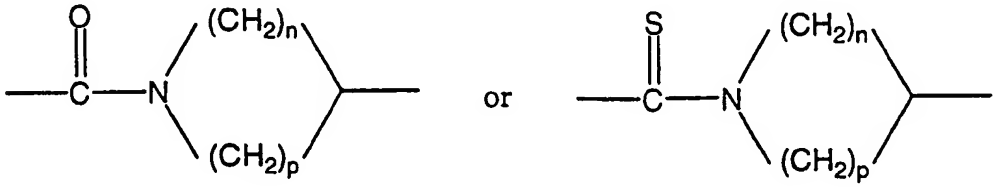
m represents 0 or 1;

A represents a group $-CONR_3-$, $-CSNR_3-$, $-SO_2NR_3-$, $-NR_3CO-$, $-NR_3CS-$,

$-NR_3SO_2-$, $-NR_3COO-$, $-OCONR_3-$ or $-NR_3CONR_3-$;

B represents C_{1-4} alkylene which can be optionally substituted with one or more groups independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl, arylC_{3-7} cycloalkyl, heteroarylC_{0-4} alkyl, $R_3R_4NC_{0-4}$ alkyl, $R_5SO_2NR_3C_{0-4}$ alkyl, $R_5CONR_3C_{0-4}$ alkyl, $R_5OCONR_3C_{0-4}$ alkyl, $R_3R_4NCONR_3C_{0-4}$ alkyl, $R_5SO_qC_{0-4}$ alkyl, $R_3R_4NSO_2C_{0-4}$ alkyl, $R_3R_4NCOC_{0-4}$ alkyl, R_5COC_{0-4} alkyl, $HOOCC_{0-4}$ alkyl, R_5OOCC_{0-4} alkyl, hydroxyC_{0-4} alkyl or R_5OC_{0-4} alkyl;

or A and B together can represent a group of formula (i) or (ii):



(i) or (ii)

R_3 and R_4 independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl or heteroarylC_{0-4} alkyl, and optionally, when A represents $-NR_3CONR_3-$, the two R_3 groups in A can be bonded together forming a C_{2-5} polymethylene chain;

R_5 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, C_{7-20} polycyclylC_{0-4} alkyl, arylC_{0-4} alkyl, arylC_{2-4} alkenyl, arylC_{3-7} cycloalkyl or heteroarylC_{0-4} alkyl;

n and p are integers 0, 1, 2 or 3 such that the sum of n plus p equals 3 to 5;

q represents 0, 1 or 2;

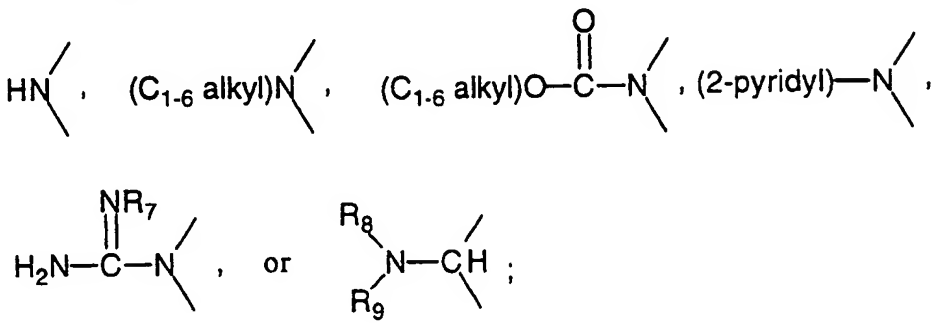
Y_1 represents N or CR_6, wherein R_6 represents hydrogen, hydroxy or C_{1-4} alkoxy;

Y_2 represents N or CH, with the proviso that when Y_1 is CR_6 then Y_2 cannot represent CH;

Y_3 represents N or CH, with the proviso that when Y_2 is N then Y_3 cannot represent N;

one of Z_1 or Z_2 represents Z and the other represents CH_2, with the proviso that when Y_3 represents N, then Z_2 represents CH_2;

Z represents a group of formula:



R_7 represents hydrogen or C_{1-4} alkyl;

R_8 and R_9 independently represent hydrogen or C_{1-4} alkyl, or they can be bonded together forming a C_{2-5} polymethylene chain;

D represents carboxy or a metabolically labile ester or amide thereof;

aryl in the above definitions represents phenyl or naphthyl which can be optionally substituted with one or more groups independently selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, carboxy, cyano, nitro, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylthio or C_{1-4} alkylcarbonylamino and wherein two substituents on adjacent carbon atoms can be bonded together forming a methylenedioxy group; and

heteroaryl in the above definitions represents an aromatic monocyclic 5- or 6-membered heterocycle or an aromatic bicyclic 9- or 10-membered heterocycle containing from one to four heteroatoms selected from N, O and S, and which can be optionally substituted with one or more groups independently selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, carboxy, cyano, nitro, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylthio or C_{1-4} alkylcarbonylamino.

Also comprised in the present invention are the addition salts of the compounds disclosed herein as well as their solvates and prodrugs. By prodrug

it is understood any precursor of a compound of formula I that is capable of being cleaved and release a compound of formula I *in vivo*.

Some compounds of formula I may contain one or more chiral centers, which may give rise to different stereoisomers. The present invention covers each of the individual stereoisomers as well as their mixtures. Moreover, some compounds of the present invention may exhibit cis/trans isomery. The present invention covers each of the geometric isomers as well as their mixtures.

The present invention also provides a pharmaceutical composition which comprises an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof in admixture with one or more pharmaceutically acceptable excipients.

The invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for the treatment or prevention of GPIIb/IIIa-mediated disorders.

The invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for inhibiting platelet aggregation.

The invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for inhibiting the binding of fibrinogen to its receptor.

The invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for the treatment or prevention of thromboembolic disorders.

The invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof for the treatment or prevention of GPIIb/IIIa-mediated disorders.

The invention also provides the use of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof for inhibiting

platelet aggregation.

The invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof for inhibiting the binding of fibrinogen to its receptor.

The invention also provides the use of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof for the treatment or prevention of thromboembolic disorders.

The invention further provides a method for the treatment or prevention of GPIIb/IIIa-mediated disorders in a mammal, which comprises administering to a mammal in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof.

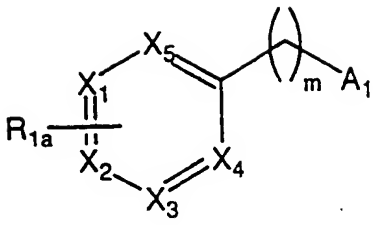
The invention further provides a method of inhibiting platelet aggregation in a mammal, which comprises administering to a mammal in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof.

The invention further provides a method of inhibiting the binding of fibrinogen to its receptor in a mammal, which comprises administering to a mammal in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof.

The invention further provides a method for the treatment or prevention of thromboembolic disorders in a mammal, which comprises administering to a mammal in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof.

The invention still further provides a process for preparing a compound of formula I, which comprises:

(a) reacting a compound of formula (II)

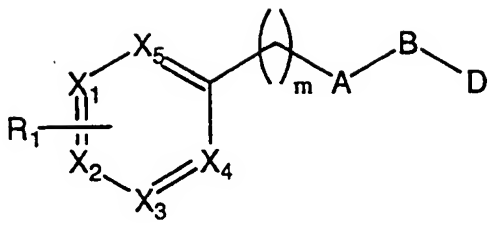


II

with a compound of formula A_2-B-D (III),

wherein B, D, m, X_1, X_2, X_3, X_4 and X_5 have the previously defined meaning, R_{1a} represents a group R_1 as defined above or a group convertible thereto, and one of A_1 or A_2 represents -COOH (or a reactive derivative thereof), $-SO_2Cl$ or -NCO and the other represents $-NHR_3$ or one of A_1 or A_2 represents -NCO and the other represents -OH, followed when necessary by the conversion of a group R_{1a} into a group R_1 and/or the removal of any protecting group that may be present; or

(b) deprotecting a compound of formula I'



I'

wherein A, B, D, m, R_1, X_1, X_2, X_3, X_4 and X_5 have the previously defined meaning but at least one of them contains a protecting group; or

(c) converting, in one or a plurality of steps, a compound of formula I into another compound of formula I; or

(d) converting a compound of formula I wherein D represents a carboxy group into a metabolically labile ester or amide thereof; and

(e) if desired, after the above steps, treating a compound of formula I with an acid or a base to give the corresponding addition salt.

Under the nomenclature used throughout this disclosure, the definitions of the substituents are to be read from left to right, so that the terminal portion of each substituent is described always in first place (i.e. to the left) and the point of attachment to the rest of the molecule is described to the right.

In the case of the "A" substituents, these are incorporated in the compounds of the invention in the order written above so that the "$(CH_2)_m$" substituent is always positioned to the left of the sequence represented by A and the "B" substituent is always positioned to the right of the sequence. For example, a suitable meaning for A is -$CONR_3$-; the "$(CH_2)_m$" substituent is linked to the carbonyl moiety of the amide group and the "B" substituent is linked to the nitrogen atom of the amide.

Moreover, when in any of the substituents a C_0 alkyl group is included, this means that the alkyl group may not be present; thus, for example, a C_{3-7} cycloalkylC_0 alkyl group means a C_{3-7} cycloalkyl group, an arylC_0 alkyl group means an aryl group, and a $R_3R_4NC_0$ alkyl group means a R_3R_4N group.

In the above definitions, the term C_{1-n} alkyl, as a group or part of a

group, means a linear or branched alkyl group that contains from 1 to n carbon atoms. Therefore, when n is 4 it includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, and *tert*-butyl. When n is 6 it includes, among others, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, neopentyl and hexyl. As stated above, a C_{0-n} alkyl group additionally indicates that no alkyl group need be present (i.e., that a covalent bond is present).

A C_{2-n} alkenyl group means a linear or branched alkyl group having from 2 to n carbon atoms and having in addition one or more double bonds. When n is 6, examples include among others ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, and 5-hexenyl.

A C_{2-n} alkynyl group means a linear or branched alkyl group having from 2 to n carbon atoms and having in addition one or more triple bonds. When n is 6, examples include among others ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, and 5-hexynyl.

The term halogen or its abbreviation halo means fluoro, chloro, bromo or iodo.

The term C_{1-n} haloalkyl means a group resulting from the substitution of one or more hydrogen atoms of a C_{1-n} alkyl group by one or more halogen atoms (i.e. fluorine, chlorine, bromine or iodine), which can be the same or different. When n is 6, examples include trifluoromethyl, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, 1- and 2-chloroethyl, 1- and 2-fluoroethyl, 1- and 2-bromoethyl, 1- and 2-iodoethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, pentafluoroethyl, 1-, 2- and 3-fluoropropyl, 1-, 2- and 3-chloropropyl, 3,3,3-trifluoropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 1-, 2-, 3- and 4-fluorobutyl, 1-, 2-, 3- and 4-chlorobutyl, nonafluorobutyl, 1-, 2-, 3-, 4- and 5-fluoropentyl, 1-, 2-, 3-, 4- and 5-chloropentyl, 1-, 2-, 3-, 4-, 5- and 6-fluorohexyl, and 1-, 2-, 3-, 4-, 5- and 6-chlorohexyl.

The term C_{3-7} cycloalkyl, as a group or part of a group, represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

A C_{1-4} alkylene group means methylene, ethylene, propylene or butylene, which can be optionally substituted as described above.

A C_{2-5} polymethylene chain means ethylene, propylene, butylene or pentylene.

The term C_{1-n} alkoxy means a group derived from the union of a C_{1-n} alkyl group to an oxygen atom of an ether functional group. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, pentyloxy and hexyloxy.

A C_{1-4} haloalkoxy group means a group resulting from the substitution of one or more hydrogen atoms of a C_{1-4} alkoxy group by one or more halogen atoms, which can be the same or different. Examples include trifluoromethoxy, fluoromethoxy, 1- and 2-chloroethoxy, 1- and 2-fluoroethoxy, 1- and 2-iodoethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, 1-, 2- and 3-fluoropropoxy, 1-, 2- and 3-chloropropoxy, 2,2,3,3,3-pentafluoropropoxy, heptafluoropropoxy, 1-, 2-, 3- and 4-fluorobutoxy, and nonafluorobutoxy.

A C_{1-4} alkylamino or C_{1-4} dialkylamino group means a group resulting from the substitution of one or two hydrogen atoms, respectively, of an amino group by one or two C_{1-4} alkyl groups, which can be the same or different. Examples include methylamino, dimethylamino, ethylamino, diethylamino, ethylmethylamino, propylamino, dipropylamino, isopropylamino, diisopropylamino and butylamino.

A C_{1-4} alkylcarbonyl group represents a group resulting from the union of a C_{1-4} alkyl group to a carbonyl group. Examples include acetyl, propionyl, isopropionyl, and butanoyl.

A C_{1-4} alkylcarbonyloxy group represents a group resulting from the union of a C_{1-4} alkylcarbonyl group to an oxygen atom of an ether functional group. Examples include acetyloxy, propionyloxy, isopropionyloxy, and butanoyloxy.

A C_{1-4} alkoxycarbonyl group represents a group resulting from the union of a C_{1-4} alkoxy group to a carbonyl group. Examples include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, *sec*-butoxycarbonyl and *tert*-butoxycarbonyl.

A C_{1-4} alkylsulfonyl group represents a group resulting from the union of a C_{1-4} alkyl group to a sulfonyl group. Examples include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, *sec*-butylsulfonyl, and *tert*-butylsulfonyl.

A C_{1-4} alkylsulfinyl group represents a group resulting from the union of a C_{1-4} alkyl group to a sulfinyl group. Examples include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, isobutylsulfinyl, *sec*-butylsulfinyl, and *tert*-butylsulfinyl.

A C_{1-4} alkylthio group represents a group resulting from the union of a C_{1-4} alkyl group to a sulphur atom of a thioether functional group. Examples include methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, *sec*-butylthio, and *tert*-butylthio.

A C_{1-4} alkylcarbonylamino group represents a group resulting from the substitution of a hydrogen atom of an amino group by a C_{1-4} alkylcarbonyl group. Examples include acetamido, propanamido and isopropanamido.

The term aryl, as a group or part of a group, represents phenyl or naphthyl, or phenyl or naphthyl substituted with one or more, preferably from one to three, groups independently selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, carboxy, cyano, nitro, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylthio or C_{1-4} alkylcarbonylamino. When there are more than one substituent, these can be the same or different and can be placed on any available position of the aryl group. Moreover, two of the substituents on an aryl group can form together a methylenedioxy group, thus giving rise to a 1,3-benzodioxole ring.

An aryl-C_{0-4} alkyl group represents a group resulting from the substitution of one hydrogen atom of a C_{0-4} alkyl group by an aryl group as defined above. As stated above, the case arylC_0 alkyl corresponds to an aryl group. Examples include among others, phenyl, naphthyl, benzyl, 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl, 4-phenylbutyl, 3-phenylbutyl, 2-phenylbutyl and 1-phenylbutyl, wherein the

phenyl and naphthyl groups can be substituted as described above in the definition of an aryl group.

The term heteroaryl, as a group or part of a group, represents any radical from an aromatic monocyclic 5- or 6-membered or aromatic bicyclic 9- or 10-membered heterocycle containing from one to four heteroatoms selected from N, O and S and which is stable and available by conventional chemical synthesis. Examples of aromatic monocyclic heterocycles include thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, pyridine, pyrazine, pyrimidine, and pyridazine. Examples of bicyclic heteroaryl groups include benzimidazole, benzofuran, indole, isoindole, benzothiophene, benzothiazole, quinoline, isoquinoline, phthalazine, quinazoline, quinoxaline, cinnoline, naphthyridine, indazole, imidazopyridine, imidazopyrimidine, imidazopyrazine, imidazopyridazine, pyrazolopyrazine, pyrazolopyridine and pyrazolopyrimidine. All these rings can be optionally substituted with one or more, preferably from one to three, groups as described above.

A C_{7-20} polycyclyl group means any fused or bridged polycyclic system containing from 7 to 20 carbon atoms, which can optionally contain one or more insaturations and which can be optionally substituted with one or more, preferably from one to three, groups independently selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, carboxy, cyano, nitro, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylthio or C_{1-4} alkylcarbonylamino. When there are more than one substituent, these can be the same or different and can be placed on any available position of the polycyclic system. More preferably, polycyclic system refers to fused or bridged bi- or tricyclic systems containing from 7 to 15 carbon atoms. Examples thereof include decaline, camphor, adamantyl and norbornyl.

In the compounds of the present invention, group D represents a carboxy group or a metabolically labile ester or amide thereof. By metabolically labile it is understood any group that is capable of being cleaved *in vivo*,

releasing the acid group and which thus act as prodrugs thereof. Examples of metabolically labile esters include C_{1-6} alkyl esters, for example methyl, ethyl, propyl, isopropyl ester; C_{1-6} alkoxyC_{1-4} alkyl esters, for example methoxymethyl, 2-methoxyethyl ester; haloC_{1-4} alkyl esters, for example 2-iodoethyl, 2,2,2-trichloroethyl ester; C_{1-6} alkylcarbonyloxyC_{1-4} alkyl esters, for example acetoxymethyl, 1-acetoxyethyl or pivaloyloxymethyl ester; arylC_{1-4} alkyl esters, for example benzyl ester; arylcarbonyloxyC_{1-4} alkyl esters, for example benzoyloxymethyl or 1-benzoyloxyethyl ester; C_{3-7} cycloalkylcarbonyloxyC_{1-4} alkyl esters; C_{1-6} alkoxycarbonyloxy C_{1-4} alkyl esters, for example 1-ethoxycarbonyloxyethyl or 1-methoxycarbonyloxyethyl ester; C_{3-7} cycloalkyloxycarbonyloxyC_{1-4} alkyl esters; C_{1-6} alkoxycarbonylC_{1-4} alkyl esters; C_{3-7} cycloalkyloxycarbonylC_{1-4} alkyl esters; C_{1-6} alkylcarbonylaminoC_{1-4} alkyl esters; C_{3-7} cycloalkylcarbonylaminoC_{1-4} alkyl esters; and aminoC_{1-4} alkyl esters (wherein the amino group can be optionally substituted), for example aminomethyl or 2-N,N-dimethylaminoethyl ester. Examples of metabolically labile amides include amides formed with ammonia and amines such as C_{1-6} alkylamines, for example methyl- or ethylamine; diC_{1-6} alkylamines, for example dimethylamine or ethylmethylamine; C_{1-6} alkoxyC_{1-6} alkylamines, for example methoxyethylamine; arylC_{1-4} alkylamines, for example benzylamine; and amino acids, for example glycine, or esters thereof.

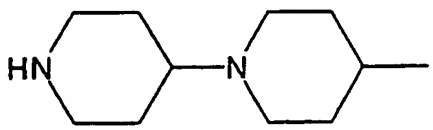
Although the present invention includes all the compounds described above, preferred compounds of the invention are those compounds described above of formula I wherein, independently or in any compatible combination:

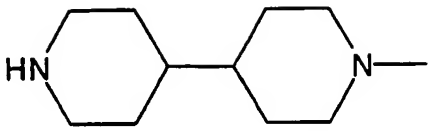
X_2 represents C substituted with the group R_1; and/or

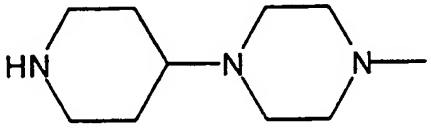
X_1, X_3, X_4 and X_5 represent CR_2 or one of X_1, X_3, X_4 and X_5 represents N and the other represent CR_2; and/or

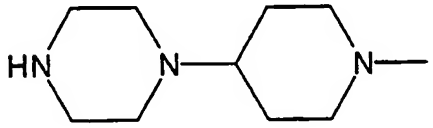
m represents 0; and/or

R_1 represents a group selected from:

(a) 

(b) 

(c) 

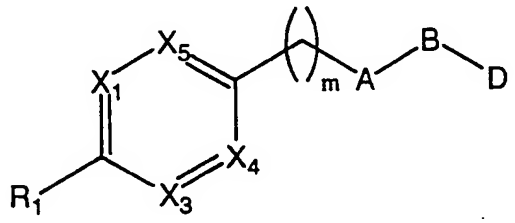
(d) 

; and/or

A represents $-CONR_3-$; and/or

B represents ethylene which can be optionally substituted, as described above.

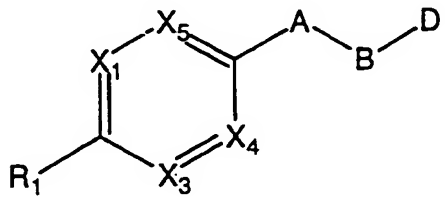
Accordingly, a preferred class of compounds of the present invention are those compounds of formula I wherein X_2 represents C substituted with the group R_1, that is compounds of formula **Ia**:



Ia

wherein X_1, X_3, X_4, X_5, R_1, m, A, B and D are as defined above in connection with formula **I**.

A more preferred class of compounds of the present invention are those compounds of formula **Ia** wherein m represents 0, that is compounds of formula **Ib**:



Ib

wherein X_1, X_3, X_4, X_5, R_1, A, B and D are as defined above.

A still more preferred class of compounds of the present invention are those compounds of formula **Ib** wherein:

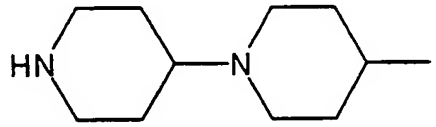
X_1, X_3, X_4 and X_5 represent CR_2 or one of X_1, X_3, X_4 and X_5 represents N and the other represent CR_2; and

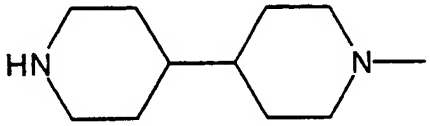
R_1, R_2, A, B and D are as defined above.

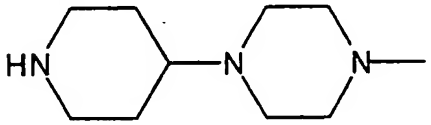
An even more preferred class of compounds of the present invention are those compounds of formula **Ib** wherein:

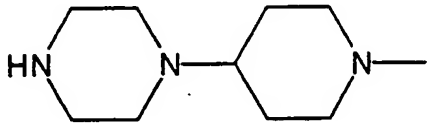
X_1, X_3, X_4 and X_5 represent CR_2 or one of X_1, X_3, X_4 and X_5 represents N and the other represent CR_2;

R_1 represents a group selected from:

(a) 

(b) 

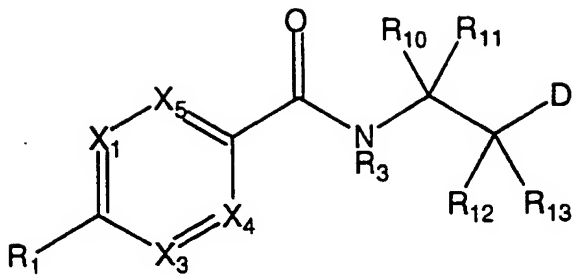
(c) 

(d) 

; and

R_2, A, B and D are as defined above.

A particularly preferred class of compounds of the present invention are those compounds of formula **Ib** wherein additionally A represents $-CONR_3-$ and B represents ethylene which can be optionally susbtituted, that is compounds of formula **Ic**:



Ic

wherein:

X_1, X_3, X_4 and X_5 represent CR_2 or one of X_1, X_3, X_4 and X_5 represents N and the other represent CR_2;

R_1 represents a group selected from (a)-(d);

R_{10}, R_{11}, R_{12} and R_{13} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl, arylC_{3-7} cycloalkyl, heteroarylC_{0-4} alkyl, $R_3R_4NC_{0-4}$ alkyl, $R_5SO_2NR_3C_{0-4}$ alkyl, $R_5CONR_3C_{0-4}$ alkyl, $R_5OCONR_3C_{0-4}$ alkyl, $R_3R_4NCONR_3C_{0-4}$ alkyl, $R_5SO_qC_{0-4}$ alkyl, $R_3R_4NSO_2C_{0-4}$ alkyl, $R_3R_4NCOC_{0-4}$ alkyl, R_5COC_{0-4} alkyl, $HOOCC_{0-4}$ alkyl, R_5OOCC_{0-4} alkyl, hydroxyC_{0-4} alkyl or R_5OC_{0-4} alkyl; and

R_2, R_3, R_4, R_5, q and D are as defined above.

A still more particularly preferred class of compounds of the present invention are those compounds of formula Ic wherein:

X_1, X_3, X_4 and X_5 represent CR_2 or one of X_1, X_3, X_4 and X_5 represents N and the other represent CR_2;

R_1 represents a group selected from (a)-(d);

R_{10} and R_{11} represent hydrogen;

one of R_{12} or R_{13} represents hydrogen and the other represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl, arylC_{3-7} cycloalkyl, heteroarylC_{0-4} alkyl, $R_3R_4NC_{0-4}$ alkyl, $R_5SO_2NR_3C_{0-4}$ alkyl, $R_5CONR_3C_{0-4}$ alkyl, $R_5OCONR_3C_{0-4}$ alkyl, $R_3R_4NCONR_3C_{0-4}$ alkyl, $R_5SO_qC_{0-4}$ alkyl, $R_3R_4NSO_2C_{0-4}$ alkyl, $R_3R_4NCOC_{0-4}$ alkyl, R_5COC_{0-4} alkyl, $HOOCC_{0-4}$ alkyl, R_5OOCC_{0-4} alkyl, hydroxyC_{0-4} alkyl or R_5OC_{0-4} alkyl; and

R_2, R_3, R_4, R_5, q and D are as defined above.

The compounds of formula I contain one or more basic nitrogen atoms and may contain one or more acid protons and, consequently, they can form salts with acids and bases both organic and inorganic, which salts are also included in the present invention. There is no limitation on the nature of these salts, provided that, when used for therapeutic purposes, they are pharmaceutically acceptable. Examples of these salts include: salts with inorganic cations such as sodium, potassium, calcium, magnesium, lithium, aluminium, zinc, etc; and salts formed with pharmaceutically acceptable amines such as ammonia, alkylamines, hydroxyalkylamines, lysine, arginine, N-methylglucamine, procaine and the like; salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, nitric acid, perchloric acid, sulfuric acid or phosphoric acid; and salts with organic acids, such as methanesulfonic acid, trifluoromethanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, fumaric acid, oxalic acid, maleic acid, citric acid, succinic acid, tartaric acid; as well as other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by reacting the compound of formula I with a sufficient amount of the desired acid or base to produce a salt in the conventional manner. Alternatively, the compound of formula I in free form can be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process. Free compounds of formula I and their salts differ in certain physicochemical properties, such as solubility, but they are equivalent for the purposes of the invention.

The compounds of the present invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for the purposes of the invention.

Some compounds of the present invention can exist as different diastereoisomers and/or optical isomers. Diastereoisomers can be separated by conventional techniques such as chromatography or fractional crystallization. The optical isomers can be resolved using any of the conventional techniques of optical resolution to give optically pure isomers. Such a resolution can be

performed in any chiral synthetic intermediate as well as in the products of general formula I. Optical resolution techniques include separation by chromatography on a chiral phase or formation of a diastereoisomeric pair, resolution and subsequent recovery of the two enantiomers. The optically pure isomers can also be individually obtained using enantiospecific synthesis. The present invention covers each of the individual isomers and their mixtures (e.g. racemic mixtures), whether as obtained by synthesis or by physically mixing them up.

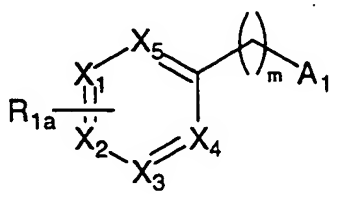
Furthermore, some of the compounds of the present invention may exhibit cis/trans isomery. The present invention covers each of the geometric isomers and the mixtures thereof.

Some compounds of the present invention may also exhibit tautomery, for example those compounds containing an amidino group. All the possible tautomer forms as well as their mixtures are encompassed by the present invention.

The present invention also provides processes for preparing a compound of formula I. The compounds of formula I may be prepared using the methods described below. It will be apparent to those skilled in the art that the precise method used for the preparation of a given compound may vary depending on its chemical structure. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. Moreover, in the majority of the processes described below it will be desirable or necessary to protect reactive or labile groups using conventional protecting groups, for example the groups described below. Both the nature of these protecting groups and the procedures for their introduction and removal are well known in the art (see for example Greene T.W., "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, 1981). In the schemes provided below, the nomenclature defined above in relation to formula I has been used to designate without distinction a substituent or group as defined in formula I or the same substituent or group in protected form.

In general, the compounds of formula I can be obtained through

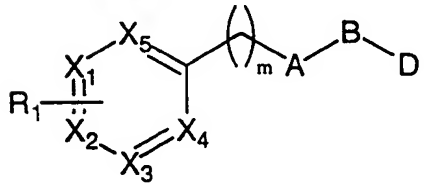
formation of the amide, sulfonamide, carbamate or urea linkage represented by group A in formula I, by reacting a compound of formula II with a compound of formula III, as shown in the following scheme:



II

i) A_2-B-D III

ii) (optional) conversion of those substituents that are present as precursor groups and/or deprotection



I

wherein:

one of A_1 and A_2 represents a group -COOH (or a reactive derivative thereof), a group $-SO_2Cl$ or a group -NCO and the other represents a group $-NHR_3$, or one of A_1 and A_2 represents a group -NCO and the other represents a group -OH;

the group R_{1a} represents a group R_1 or a precursor thereof (i.e. a group convertible thereto); and

the groups A, B, D, m, R_1, R_3, X_1, X_2, X_3, X_4 and X_5 are as described above.

For this process, any known method for preparing amide, sulfonamide, carbamate or urea bonds can be used.

For example, an amide can be prepared by reaction of a carboxylic acid with an amine in the presence of a suitable condensing agent, such as a diimide (e.g. dicyclohexylcarbodiimide), alone or associated with 1-

hydroxybenzotriazole or N-hydroxysuccinimide, in a suitable solvent. As examples of suitable solvents we can mention substituted amides such as dimethylformamide; ethers such as dioxane and tetrahydrofuran; and halogenated hydrocarbons such as dichloromethane and chloroform. When the amine is used as an addition salt, for example the hydrochloride, the reaction is carried out in the presence of a base, such as triethylamine.

Alternatively, the amide bond can be prepared by reacting an amine with a reactive derivative of a carboxylic acid, such as the acid chloride, anhydride or mixed anhydride. In this case, the reaction is carried out in the presence of a proton scavenger base, for example pyridine or triethylamine, in a suitable solvent, or alternatively the proton scavenger amine itself can be used as the solvent. As examples of suitable solvents we can mention halogenated hydrocarbons such as dichloromethane and chloroform; ethers such as diethyl ether, dioxane and tetrahydrofuran; and aromatic hydrocarbons such as benzene and toluene.

A sulfonamide linkage can be prepared by reacting an amine with a sulfonyl chloride under similar experimental conditions to those described above for the reaction of an amine with an acid chloride.

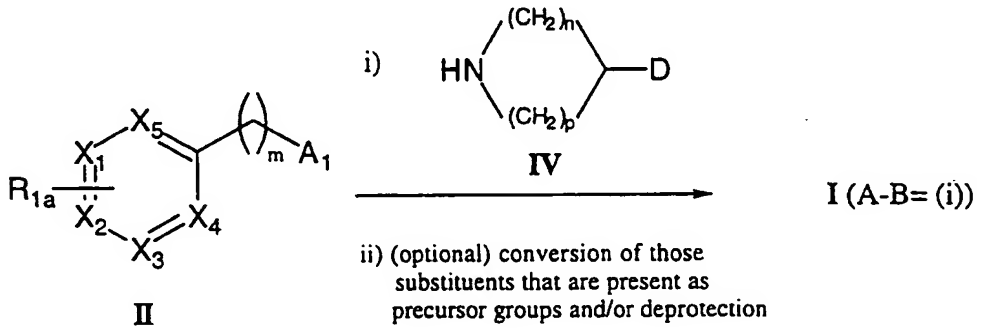
The urea function can be prepared by reaction of an isocyanate with an amine under similar experimental conditions to those described above for the reaction of an amine with an acid chloride. The isocyanate may have been previously prepared or may be generated *in situ* from the corresponding carboxylic acid by conventional procedures, for example by treatment with diphenylphosphorylazide in the presence of triethylamine.

When in a compound of formula I the substituent A represents a carbamate -NR_3COO-, this can be prepared by reaction of a compound of formula II wherein A_1 represents -NCO with an alcohol de formula III wherein A_2 represents -OH. Carbamates of formula -$OCONR_3$- can be prepared by reaction of a compound of formula II wherein A_1 represents -OH with an isocyanate of formula III wherein A_2 represents -NCO. Here, isocyanates may also have been previously prepared or may be generated *in situ* from the corresponding carboxylic acid by treatment with diphenylphosphorylazide in

the presence of triethylamine.

When in a compound of formula I the substituent A represents a thioamide, this can be prepared by reacting a thiocarboxylic acid with an amine under similar experimental conditions to those described above for the reaction of an amine with a carboxylic acid. Alternatively, thioamides may be prepared from the corresponding amides by treatment with any known thiation reagent, such as hydrogen sulfide, phosphorous pentasulfide or Lawesson's reagent (*p*-methoxyphenylthiophosphine disulfide) in an inert apolar solvent such as toluene.

When in a compound of formula I A-B represents a group of formula (i), these compounds may be prepared by reaction of a compound of formula II wherein A_1 represents -COOH or a reactive derivative thereof with an amine of formula IV in the same experimental conditions disclosed above, as shown in the following scheme:



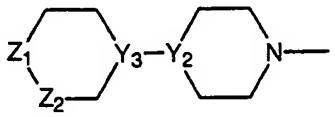
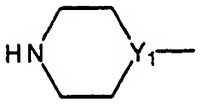
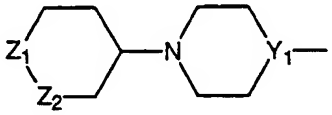
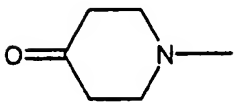
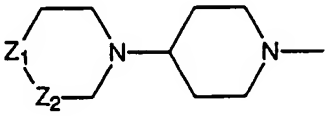
wherein A_1 represents -COOH, or a reactive derivative thereof; and D, m, n, p, R_{1a}, X_1, X_2, X_3, X_4 and X_5 are as defined above.

The compounds of formula I wherein A-B represents a group of formula (ii) can be prepared from the corresponding amides (i.e., a compound of formula I wherein A-B= (i)) by thiation, as described above.

In the starting products of formulae II, III and IV, the different substituents present in the compounds of formula I can already be present as such or can be present as precursor groups, i.e. can be present as groups which can be easily converted later to the substituent in a compound of formula I.

When any of the substituents, particularly group R_1, is in the form of a precursor group, it will be necessary to transform these precursor groups into the substituents present in I after the reaction of II with III or II with IV. These conversions are carried out in one or more steps using widely known procedures of organic synthesis, such as those mentioned below and those disclosed in the examples.

Thus, when in a compound of formula II R_{1a} represents a precursor of the subtituent R_1 in formula I, after the reaction of II with III or IV it will be necessary to convert this group R_{1a} into R_1. Without intending to be a limiting list, some of these conversions are exemplified in the following table:

R_{1a}		R_1
F, Br, Cl—	A	
	B	
	C	

Conversion A can be carried out in dimethylsulfoxide as solvent in the presence of diisopropylethylamine and heating, or in pyridine at reflux.

Conversions B and C are carried out under standard reductive amination conditions, for example by treatment with sodium triacetoxyborohydride in tetrahydrofuran/acetic acid.

The compounds of formula II wherein R_{1a} already represents a group R_1 as present in formula I can be prepared from a compound of formula II

wherein R_{1a} represents a precursor of R_1 using the same conversions disclosed above, namely conversions A-C. The coupling of a compound II of this kind wherein R_{1a} already represents a group R_1 with a compound III or IV will directly lead to a compound of formula I, subject to removal of any protecting group that might be present.

Some compounds of formula I can also be obtained by interconversion from another compound of formula I in one or more steps, using widely employed procedures of chemical synthesis.

Thus, a substituent R_2 in a group X_i or a substituent of the alkylene chain represented by B can be converted into other groups, thus generating further compounds of formula I. For example, an amino group can be easily converted into an amide, sulfonamide, carbamate or urea using standard procedures, such as those described above to prepare substituent A; an amino group can be alkylated for example by treatment with a suitable alkylating agent; a carboxy group can be easily converted into an ester or amide using the procedures described above; a hydroxy group can be converted into an ether group by reaction for example with an alcohol in the presence of a dehydrating agent; an ester, amide or ether group may be hydrolyzed under acidic or basic conditions to give the corresponding carboxy or hydroxy groups; a nitro group can be reduced, for example by hydrogenation in the presence of a suitable catalyst such as Pd/C, to afford an amino group; a thioether group may be oxidized under standard conditions to give the corresponding sulfoxide or sulfone.

Other interconversions between compounds of formula I may involve transformations of the group A. For example, an amide can be converted into a thioamide using a suitable thiation reagent, such as those described above. Moreover, the nitrogen atom of an amide, sulfonamide, carbamate or urea can also be N-alkylated using a suitable alkylating agent.

All the above types of transformations are widely described in the literature and are carried out under the standard experimental conditions used in organic synthesis for these type of reactions. Some of them are described in greater detail in the examples below.

All these interconversion reactions between different substituents can be carried out upon the final compounds of formula I as well as upon any synthetic intermediate thereof, for example upon compounds of formulae II or III.

As will be evident to those skilled in the art, in order to carry out the reaction between II and a compound of formulae III or IV as well as for any other transformation, for example the conversion of R_{1a} into R_1 or the interconversions between substituents, it will be necessary or convenient that the remaining reactive functional groups that may be present in these compounds are in duly protected form. As protecting groups any conventional protecting group known in the art can be employed, for example those described in Greene T.W., "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, 1981. For example, as protecting groups of an amino or amidino function, the groups *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and fluorenylmethoxycarbonyl (Fmoc) can be used. Carboxy groups can be protected for example as C_{1-4} alkyl esters, such as methyl, ethyl or *tert*-butyl esters, or arylC_{1-4} alkyl esters, such as benzyl ester.

Whenever a protecting group is present, it will be necessary a subsequent deprotection step in order to remove this protecting group. Deprotection is carried out under standard conditions, for example those disclosed in the above-mentioned reference. It should be noted here that some compounds bearing a protecting group fall within the scope of formula I, for example those compounds wherein the carboxy group represented by D is protected in the form of an ester.

A compound of the present invention can also be converted to a metabolically labile ester or amide thereof using standard methods, for example by esterification of a compound of formula I under usual experimental conditions or by reaction of an acid, or a reactive derivative thereof, with the desired amine as described above for the reaction of II with III.

The salts of the compounds of formula I can be prepared by conventional methods, for example by treatment of a compound of formula I with an acid such as hydrochloric acid, sulfuric acid, nitric acid, oxalic acid or

methanesulfonic acid, or by treatment with a base such as sodium hydroxide or potassium hydroxide.

The compounds of formulae II, III and IV are commercially available, are widely described in the literature or can be prepared by methods analogous to those described starting from commercially available products. Some of these methods are disclosed in greater detail in the examples below.

As mentioned above, the compounds of the present invention act by inhibiting the binding of fibrinogen to its receptor (GP IIb/IIIa) and thus may be useful for the treatment of GPIIb/IIIa-mediated disorders. Since GPIIb/IIIa is involved in platelet aggregation processes, the compounds of the invention are useful as preventive and therapeutic agents for the treatment of disorders requiring the inhibition of platelet aggregation. This includes the treatment or prevention of thromboembolic disorders such as arterial or venous cardiovascular or cerebrovascular thromboembolic disorders including, but not limited to, venous thrombosis, deep vein thrombosis, thrombophlebitis, pulmonary embolism, arterial embolism, renal embolism, cerebral embolism, transient ischemic attack, stroke, myocardial infarction, unstable and stable angina and atherosclerosis. Other applications of the compounds of the present invention include the prevention of thromboembolism and reocclusion during and after thrombolytic therapy, and the prevention of thromboembolism and reocclusion after angioplasty of the coronary and other arteries or after coronary artery bypass procedures. Additionally, the compounds of the present invention may be useful for the treatment or prevention of any other GPIIb/IIIa-mediated disorder.

There are other integrins structurally related to the fibrinogen receptor that are able to recognize the sequence Arg-Gly-Asp, for which reason the compounds of the present invention might also inhibit the adhesion processes where these other integrins are involved. Therefore, the compounds of the present invention might find additional utility as suppressors of the metastasis of cancerous cells in the treatment of cancer, and as inhibitors of bone resorption in the treatment of bone disorders such as osteoporosis, hypercalcemia, osteopenia due to bone metastasis, periodontal disease,

hyperparathyroidism, periarticular erosions in rheumatoid arthritis and Paget's disease.

The compounds of the present invention can be administered in combination with one or more additional therapeutic agents commonly used

for the treatment of the above-mentioned disorders, for example other platelet antiaggregants (such as aspirin, triflusal, ticlopidine, thromboxane inhibitors, thromboxan synthase inhibitors), thrombolytic agents (such as tPA and its derivatives, anistreplase, streptokinase, urokinase, prourokinase), or anticoagulant agents (such as warfarin and heparin). The present invention thus provides also the use of a compound of formula I in combination with one or more therapeutic agents, such as those cited above.

According to the activity of the compounds herein disclosed, the present invention further provides compositions that comprise a compound of the invention together with one or more excipients. The compounds of the present invention can be administered in different pharmaceutical preparations, the precise nature of which will depend, as it is well known, upon the chosen route of administration and the nature of the pathology to be treated.

Thus, solid compositions, according to the present invention, for oral administration include compressed tablets, dispersible powders, granules and capsules. In tablets, the active component is admixed with at least one inert diluent such as lactose, starch, mannitol, microcrystalline cellulose or calcium phosphate; granulating and disintegrating agents, for example corn starch, gelatine, microcrystalline cellulose or polyvinylpyrrolidone; and lubricating agents for example magnesium stearate, stearic acid or talc. The tablets may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and, thereby, provide a sustained action over a longer period. Gastric film-coated or enteric film-coated tablets can be made with sugar, gelatin, hydroxypropylcellulose, or acrylic resins. Tablets with a sustained action may also be obtained using an excipient which provides regressive osmosis, such as the galacturonic acid polymers. Formulations for oral use may also be presented as hard capsules of absorbable material, such as gelatin, wherein the active ingredient is mixed with an inert solid diluent and lubricating agents, or pasty materials, such as ethoxylated saturated glycerides. Soft gelatin capsules are also possible, wherein the active ingredient is mixed

with water or an oily medium, for example peanut oil, liquid paraffin or olive oil.

Dispersible powders and granules suitable for the preparation of a suspension by the addition of water provide the active ingredient in admixture with dispersing or wetting agents; suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, xantham gum, gum acacia; and one or more preservatives, such as methyl or *n*-propyl-*p*-hydroxybenzoate. Additional excipients, for example sweetening, flavoring and coloring agents may also be present.

Liquid compositions for oral administration include emulsions, solutions, suspensions, syrups and elixirs containing commonly used inert diluents, such as distilled water, ethanol, sorbitol, glycerol, or propylene glycol. Such compositions may also comprise adjuvants such as wetting agents, suspending agents, sweetening, flavoring, perfuming, preserving agents and buffers.

Preparations for injection, according to the present invention, for parenteral administration by bolus injection or continuous infusion include sterile aqueous or non-aqueous solutions, suspensions or emulsions, in a non-toxic parentally-acceptable diluent or solvent. Examples of aqueous solvents or suspending media are distilled water for injection, Ringer's solution, and isotonic sodium chloride solution. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, or alcohols such as ethanol. These compositions may also include adjuvants such as wetting, preserving, emulsifying and dispersing agents. They may be sterilized by any known method or manufactured in the form of sterile solid compositions which can be dissolved in sterile water or some other sterile injectable medium immediately before use. When all of the components are sterile, the injectables will maintain the sterility if they are manufactured in sterile environment.

As stated above, the compounds of the present invention may be

administered in combination with one or more additional therapeutic agents such as platelet aggregation inhibitors, thrombolytic agents, or anticoagulant agents. The present invention thus provides a combination comprising a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof together with one or more therapeutic agents; the therapeutic agents are preferably selected from a platelet aggregation inhibitor, a thrombolytic agent or an anticoagulant agent.

The individual components of such combinations may be formulated together in the same dosage unit or may be administered separately, either simultaneously or sequentially, in which case it is not necessary that all components be administered by the same route. The present invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof in combination with one or more therapeutic agents and one or more pharmaceutically acceptable excipients.

Also provided is a method for the treatment or prevention of a thromboembolic disorder in a mammal, which comprises administering to a mammal in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof in combination with one or more therapeutic agents. Preferred is the method where the therapeutic agents are selected from a platelet aggregation inhibitor, a thrombolytic agent or an anticoagulant agent.

The dosage and frequency of dose may vary depending upon the nature and severity of the disease, symptoms, age and body weight of the patient, as well as upon the route of administration. In general, the compounds of the present invention may be administered orally at a dosage ranging from 0.01 mg/Kg/day to 20 mg/Kg/day, which can be administered as a single dose or as divided doses.

Following are some representative preparations for tablets, capsules and injectables. They can be prepared following standard procedures and they are useful for the treatment and prevention of GPIIb/IIa-mediated disorders.

Tablets

Compound of formula I	50	mg
Dibasic calcium phosphate	125	mg
Sodium starch glycolate	10	mg
Talc	12.5	mg

Magnesium stearate	2.5	mg
	200.0	mg

Hard gelatin capsules

Compound of formula I	50	mg
Lactose	197	mg
Magnesium stearate	3	mg
	250	mg

Injectable

Compound of formula I	50	mg
Benzylic alcohol	0.05	mL
Propylene glycol	1	mL
Water to	5	mL

The activity of the compounds of the present invention as platelet aggregation inhibitors may be tested as follows:

Test 1: inhibition of ADP-induced platelet aggregation in human blood

Human blood was collected from medication-free healthy volunteers into tubes containing 3.16% sodium citrate. Platelet-rich plasma (PRP) was obtained by centrifugation of whole blood at 200 g for 10 min at 4°C. PRP was collected and the remaining blood was subjected to further centrifugation at 1700 g for 10 min to make platelet-poor plasma (PPP). PRP was adjusted to $2x10^8$ platelets/mL by diluting with PPP. Platelet aggregation was measured at 37°C by recording the increase in light transmission using a Chronolog aggregometer. Platelet aggregation was initiated by the addition of ADP (5 µM) to 360 µL of PRP under stirring. Test compounds or vehicle were added 4 min before the addition of ADP. The results are expressed as the IC_{50} value, i.e. the concentration of test compound required to produce a 50% inhibition of

platelet aggregation. The results obtained with representative compounds of the present invention are shown in Table I.

TABLE I

Compound (Example No.)	IC_{50} (nM)
1	200
6	120
20	180
23	20
26	100
27	140
29	120
30	170
45	39
50	5
56	45
59	21
61	20
62	68
73	50

Test 2: inhibition of ADP-induced platelet aggregation in an *ex vivo* model in dogs following oral administration

Blood was extracted from the jugular vein of Beagle dogs at 15 min before (basal value) and at 1, 2, 3 and 4 hours post-administration of the test compounds. Test compounds were administered p.o. in capsules.

Following each extraction, platelet activity was determined using

essentially the same protocol described in test 1.

Representative compounds were tested in this model and were found to be active at a dose of 5 mg/kg p.o., or much less.

The following examples illustrate, but do not limit, the scope of the present invention. The following abbreviations have been used throughout the examples:

DMF: dimethylformamide
EtOAc: ethyl acetate
DMSO: dimethylsulfoxide
Hex: hexane
THF: tetrahydrofuran
BOC_2O: di*tert*-butyl carbonate
NMP: N-methylpyrrolidone
NEt_3: triethylamine
MeOH: methanol
EtOH: ethanol
n-BuOH: n-butanol
DMAP: dimethylaminopyridine

Reference example 1

4-[1'-(*Tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoic acid

a) Methyl 4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoate

A mixture of 1-(*tert*-butoxycarbonyl)-4,4'-bipiperidine (7 g, 27 mmol; prepared from 4,4'-bipiperidine dihydrochloride and BOC_2O) and methyl 4-fluorobenzoate (4.17 g, 27 mmol) in NMP (60 mL) was heated at 130 °C for 2 days. The solvent was removed and the residue was partitioned between 0.5N NaOH and $CHCl_3$. The organic layer was concentrated, and the residue was taken up in boiling EtOAc (100 mL) and was allowed to crystallize in the freezer overnight. Crystals were collected by filtration to afford the desired product (5.7 g, 54%).

b) Title compound

A solution of the product obtained in step a) (5.7 g, 14 mmol) in EtOH (75 mL) was treated with 1N NaOH (50 mL) and the mixture was heated at 40°C overnight and finally at reflux for 3 h. EtOH was removed and the resulting residue was brought to pH 2 with 5% $NaHSO_4$ in an ice bath. The resulting precipitate was collected by filtration and dried to afford 4.22 g of the title compound (77%).

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.83 (d, J=8.9Hz, 2H), 6.91 (d, J=8.9Hz, 2H), 4.77 (broad s), 4.09 (d, J=13.1Hz, 2H), 3.92 (d, J=13.1Hz, 2H), 2.75 (m, 4H), 1.77 (m, 2H), 1.44 (s, 9H), 1.33 (m, 8H).

Reference example 2

Ethyl 3-[N-[2-amino-4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoyl]amino]propionate

a) Ethyl 3-[N-(4-fluoro-2-nitrobenzoyl)amino]propionate

To a solution of β-alanine ethyl ester hydrochloride (3.32 g, 21.6 mmol) in anhydrous DMF (25 mL), cooled in an ice bath, was added NEt_3 (3.1 mL) and the mixture was stirred at room temperature for 15 min. Next, 4-fluoro-2-nitrobenzoic acid (4 g, 21.6 mmol, prepared from 4-fluoro-2-nitrotoluene by oxidation with $Na_2Cr_2O_7/H_2SO_4$) and 1-hydroxybenzotriazole (3.2 g) were added. The resulting mixture was placed again in an ice bath and then dicyclohexylcarbodiimide (4.39 g) was added. The mixture was removed from the ice bath and was stirred at room temperature overnight. The insoluble material was filtered off and DMF was removed. The resulting crude product was taken up in $CHCl_3$, 0.5N NaOH was added and the aqueous phase was extracted 3x with $CHCl_3$. The combined organic extracts were dried and concentrated to afford a crude product. This was purified by chromatography on silica gel ($CHCl_3$-MeOH, 2%), yielding 5.8 g of the desired product (94%).

b) Ethyl 3-[N-[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]-2-nitrobenzoyl]amino]propionate

To a solution of the product obtained in step a) (4.5 g, 15.8 mmol) and 1-(*tert*-butoxycarbonyl)-4,4'-bipiperidine (4.27 g, 15.9 mmol) in anhydrous DMSO (25 mL) was added diisopropylethylamine (2.8 mL) and the mixture was heated

at 130°C overnight. DMSO was removed and the resulting crude product was purified by chromatography on silica gel (EtOAc:Hex, 9:1) to yield 5.9 g of the desired product (70%) as a brown oil.

c) Title compound

To a solution of the compound obtained in step b) (5.9 g, 11 mmol) in MeOH (150 mL) was added 10% Pd/C catalyst (0.5 g) and the mixture was hydrogenated at room temperature overnight. More MeOH (200 mL) was added, the catalyst was filtered off and the resulting solution was concentrated to afford 5.4 g of the title compound.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 7.19 (d, J=8.9Hz, 1H), 6.53 (t, J=5.9Hz, 1H), 6.21 (dd, J=8.8Hz, J=2.4Hz, 1H), 6.05 (s, 1H), 5.63 (m, 1H), 4.17 (q, J=7.2Hz, 2H), 4.09 (m, 2H), 3.76 (d, J=12.9Hz, 2H), 3.63 (q, J=5.9Hz, 2H), 2.62 (m, 6H), 1.73 (m, 6H), 1.31 (s, 9H), 1.27 (t, J=7.2Hz, 3H), 1.25 (m, 4H).

Reference example 3

Ethyl 3-[N-[3-amino-4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoyl]amino]propionate

a) Ethyl 3-[N-[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]-3-nitrobenzoyl]amino]propionate

Following a similar procedure to that described in reference example 2 (steps a and b), but starting from 4-fluoro-3-nitrobenzoic acid, the desired product was obtained.

b) Title compound

Following a similar procedure to that described in reference example 2c, but starting from the compound obtained in the preceding step, the title compound was obtained.

Reference example 4

Ethyl 3-[N-[2-amino-5-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoyl]amino]propionate

Following a similar procedure to that described in reference example 2, but starting from 5-fluoro-2-nitrobenzoic acid, the title compound was obtained.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 6.93 (m, 2H), 6.71 (t, J=5.9Hz, 1H), 6.63 (d, J=8.8Hz, 1H), 5.0 (m, 1H), 4.17 (q, J=7.2Hz, 2H), 4.12 (m, 2H), 3.67 (q, J=5.9Hz, 2H), 3.46 (d, J=12.9Hz, 2H), 2.57 (m, 6H), 1.72 (m, 4H), 1.46 (s, 9H), 1.29 (t, J=7.2Hz, 3H), 1.25 (m, 6H).

Reference example 5

Methyl 3-amino-2(S)-(phenylsulfonylamino)propionate, hydrochloride

a) Nα-Phenylsulfonyl-L-asparagine

To a mixture of L-asparagine (10 g, 0.07 mol) in a solution of NaOH (3.4 g) in 50 mL of water and 50 mL of dioxane, cooled with an ice bath, was added dropwise benzenesulfonyl chloride (10.6 mL, 0.08 mol) and the reaction mixture was stirred at this temperature for 1 h. Dioxane was removed, the resulting solution was extracted with EtOAc and the aqueous phase was brought to pH=3 with concentrated HCl. The white precipitate formed was collected by filtration and washed with water, to afford 13.5 g of the desired compound.

^{1}H NMR (300MHz, D_2O) δ (TMS): 7.80 (d, J=8.4Hz, 2H), 7.56 (m, 3H), 4.66 (s), 4.17 (m, 1H), 2.64 (dd, J=15.2Hz, J=5.1Hz, 1H), 2.54 (dd, J=15.2Hz, J=7.9Hz, 1H).

b) 3-Amino-2(S)-(phenylsulfonylamino)propionic acid

To a solution of NaOH (14.7 g, 0.367 mol) in 60 mL of water, cooled to 0 °C, was added Br_2 (3.3 mL, 0.064 mol) and the resulting solution was stirred at that temperature for 5 min. Next, a solution prepared with the compound obtained in step a) (13.5 g, 0.049 mol), NaOH (3.6 g) and 45 mL of water was added, and the reaction mixture was stirred for 20 min at 0 °C and for 30 min at 90 °C. The resulting solution was allowed to cool, was acidified to pH=7 with concentrated HCl and the white solid formed was collected by filtration, to afford 4.5 g of the desired compound.

^{1}H NMR (300MHz, D_2O) δ (TMS): 7.82 (d, J=8.4Hz, 2H), 7.56 (m, 3H), 4.68 (s), 3.79 (m, 1H), 3.28 (dd, J=13.1Hz, J=4.6Hz, 1H), 3.03 (dd, J=13.1Hz, J=8.8Hz, 1H).

c) Title compound

To a solution of the compound obtained in step b) (3.5 g, 0.014 mol) in MeOH (45 mL), cooled to -20 °C, was added thionyl chloride (1.1 mL) and the

reaction mixture was stirred at room temperature for 18 h. The resulting solution was evaporated to dryness to yield 4.5 g of the title compound.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 8.24 (s, 2H), 7.96 (d, J=8.4Hz, 2H), 7.72 (d, J=8.9Hz, 1H), 7.51 (m, 3H), 4.57 (m, 1H), 3.69 (m, 2H), 3.37 (s, 3H).

Reference example 6

Methyl 3-amino-2(S)-(benzyloxycarbonylamino)propionate, hydrochloride

To a solution of 3-amino-2(S)-(benzyloxycarbonylamino)propionic acid (16.7 g, 0.014 mol) in MeOH (300 mL), cooled to -10 °C, was added thionyl chloride (5.1 mL). The temperature was then allowed to rise to 0 °C and stirring was maintained at this temperature for 3 h. The resulting solution was evaporated to dryness to yield the title compound.

^{1}H NMR (300Mhz, DMSO-d_6) δ (TMS): 8.16 (s, 2H), 7.88 (d, J=8.9Hz, 1H), 7.33 (m, 5H), 5.05 (s, 2H), 4.42 (m, 1H), 3.66 (s, 3H), 3.20 (m, 1H), 3.05 (m, 1H).

Reference example 7

Methyl 3-amino-2(S)-[(4-methoxyphenyl)sulfonylamino]propionate, hydrochloride

a) Methyl 2(S)-amino-3-(*tert*-butoxycarbonylamino)propionate

To a solution of the compound obtained in reference example 6 (19.3 g, 66 mmol) and BOC_2O (14.5 g, 66 mmol) in THF (250 mL), cooled to 0 °C, was added dropwise triethylamine (10.2 mL) and the reaction mixture was stirred at room temperature for 18 h. Next, the solvent was removed, EtOAc was added, and the resulting crude product was washed twice with 1% citric acid solution and then with 1% $NaHCO_3$ solution. The organic phase was dried and concentrated to yield 21.6 g of a crude product. This was purified by chromatography on silica gel (hexane:EtOAc, 3:2) to afford 16.6 g of methyl 2(S)-(benzyloxycarbonylamino)-3-(*tert*-butoxycarbonylamino)propionate. This was dissolved in MeOH (200 mL) and was hydrogenated over 10% Pd/C (0.68 g) at atmospheric pressure. The catalyst was filtered off and the solvent was removed to afford 8.9 g (62%) of the desired compound.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 5.03 (m, 1H), 3.73 (s, 3H), 3.57 (m, 1H), 3.46 (m, 1H), 3.23 (m, 1H), 1.44 (s, 9H).

b) Title compound

To a solution of the compound obtained in step a) (2 g, 9 mmol) and triethylamine (2.55 mL) in $CHCl_3$ (40 mL), cooled to 0 °C, was added in portions 4-methoxybenzenesulfonyl chloride (2 g, 10 mmol) and the reaction mixture was stirred at room temperature for 18 h. The resulting solution was washed with water, dried and concentrated, to afford 5 g of a crude product. This was purified by chromatography on silica gel (hexane:EtOAc, 1:1) to yield 3 g of methyl 3-(*tert*-butoxycarbonylamino)-2(S)-[(4-methoxyphenyl)sulfonylamino]-propionate. This was deprotected by treatment with HClg/dioxane 2M (30 mL) at room temperature for 2 h, which upon removal of the solvent yielded the title compound.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 8.25 (s, 2H), 7.87 (d, J=8.4Hz, 2H), 7.57 (d, J=8.9Hz, 1H), 6.91 (d, J=8.4Hz, 2H), 4.49 (m, 1H), 3.80 (s, 3H), 3.69 (m, 2H), 3.44 (s, 3H).

Reference example 8

Methyl 3-amino-2(S)-[(2-thienylcarbonyl)amino]propionate, hydrochloride

Following a similar procedure to that described in reference example 5a, but using (2-thienyl)carbonyl chloride instead of benzenesulfonyl chloride, and carrying out the degradation of the resulting amide by treatment with iodosobenzene diacetate (J. Org. Chem. 1997, 62, 6918-20) and the esterification as described in reference example 5c, the title compound was obtained.

^{1}H NMR (300MHz, $CDCl_3$+DMSO-d_6) δ (TMS): 8.75 (d, J=7.5Hz, 1H), 8.43 (s, 2H), 7.92 (m, 1H), 7.48 (m, 1H), 6.88 (m, 1H), 4.83 (m, 1H), 3.58 (s, 3H), 3.33 (m, 2H).

Reference example 9

Methyl 3-amino-2(S)-(n-butoxycarbonylamino)propionate, hydrochloride

Following a similar procedure to that described in reference example 8, but using n-butoxycarbonyl chloride instead of (2-thienyl)carbonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, DMSO-d_6+TFA) δ (TMS): 8.01 (s, 2H), 7.60 (d, J=7.5Hz, 1H), 4.37 (m, 1H), 3.94 (m, 2H), 3.63 (s, 3H), 3.17 (m, 1H), 3.04 (m, 1H), 1.52 (m, 2H), 1.27 (m, 2H), 0.83 (t, J=7.9Hz, 3H).

Reference example 10

Methyl 3-amino-2(S)-[2-(2-thienyl)acetylamino]propionate, hydrochloride

Following a similar procedure to that described in reference example 7, but using 2-(2-thienyl)acetyl chloride instead of 4-methoxybenzenesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 7.23 (m, 1H), 6.98 (m, 2H), 6.81 (m, 1H), 4.87 (m, 1H), 4.56 (m, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 3.51 (m, 2H).

Reference example 11

Methyl 3-amino-2(S)-[3-(4-fluorophenyl)ureido]propionate, hydrochloride

Following a similar procedure to that described in reference example 7, but using 4-fluorophenylisocyanate instead of 4-methoxybenzenesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 7.32 (m, 2H), 7.11 (t, J=8.3Hz, 1H), 6.91 (t, J=8.3Hz, 1H), 4.58 (m, 1H), 4.02 (s, 3H), 3.31 (m, 2H).

Reference example 12

Methyl 3-amino-2(S)-(benzylsulfonylamino)propionate, hydrochloride

Following a similar procedure to that described in reference example 7, but using benzylsulfonyl chloride instead of 4-methoxybenzenesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 7.99 (m, 3H), 7.43 (m, 2H), 7.23 (m, 3H), 4.46 (s, 2H), 4.34 (m, 1H), 3.70 (s, 3H), 3.37 (m, 2H).

Example 1

3-[N-[4-(4,4'-Bipiperidin-1-yl)benzoyl]amino]propionic acid

a) *Tert*-butyl 3-[N-[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoyl]amino]propionate

Following a similar procedure to that described in reference example 2a, but using the compound obtained in reference example 1 instead of 4-fluoro-2-nitrobenzoic acid and using β-alanine *tert*-butyl ester, the desired product was obtained (0.37 g, 56%).

b) Title compound

A solution of the compound obtained in step a) (0.37 g, 0.717 mmol) in

CH_2Cl_2 (4 mL), cooled in an ice bath, was treated with trifluoroacetic acid (4 mL). The mixture was stirred at room temperature overnight. The resulting mixture was evaporated to dryness, MeOH was added and the resulting solution was again evaporated to dryness. Finally, some diethyl ether was added and the mixture was allowed to stand in the freezer overnight. The solid formed was collected by filtration and dried to afford the title compound as the trifluoroacetate salt (265 mg, 75%).

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.70 (d, J=8.9Hz, 2H), 6.96 (d, J=8.9Hz, 2H), 4.79 (broad s), 3.91 (d, J=11.9Hz, 2H), 3.59 (t, J=6.9Hz, 2H), 3.40 (d, J=11.9Hz, 2H), 2.95 (t, J=10.1Hz, 2H), 2.78 (t, J=10.1Hz, 2H), 2.61 (t, J=6.9Hz, 2H), 2.00 (d, J=10.2Hz, 2H), 1.83 (d, J=10.2Hz, 2H), 1.41 (m, 6H). Mp: 216-217°C ($C_{20}H_{29}N_3O_3.CF_3COOH.H_2O$).

Example 2

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(methylsulfonylamino)benzoyl]amino]propionic acid

a) **Ethyl 3-[N-[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]-2-(methylsulfonylamino)benzoyl]amino]propionate**

To a solution of the compound obtained in reference example 2 (0.6 g, 1.19 mmol) in pyridine (10 mL), cooled in an ice bath, was added methanesulfonyl chloride (0.1 mL, 1.31 mmol) and the resulting mixture was stirred at room temperature overnight and then at 40°C for 2 h. Pyridine was removed and the residue was partitioned between 0.5N NaOH and $CHCl_3$ and was extracted with $CHCl_3$ (3x). The combined organic extracts were dried and concentrated to afford 1.3 g of a crude product. This was purified by chromatography on silica gel (CH_2Cl_2-MeOH, 1%), yielding 0.64 g of the desired compound (98%).

b) **3-[N-[4-[1'-(*Tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]-2-(methylsulfonylamino)benzoyl]amino]propionic acid**

Following the hydrolysis procedure described in reference example 1b, but starting from the compound obtained in step a) above and purifying the resulting product by chromatography on silica gel ($CHCl_3$:MeOH:NH_3, 10:3:1), the desired compound was obtained (0.5 g, 82%).

c) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step b) above, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.59 (d, J=8.9Hz, 1H), 7.16 (m, 1H), 6.73 (m, 1H), 4.86 (broad s), 3.92 (d, J=11.9Hz, 2H), 3.55 (t, J=6.9Hz, 2H), 3.36 (d, J=11.9Hz, 2H), 2.96 (s, 3H), 2.87 (m, 4H), 2.61 (t, J=6.9Hz, 2H), 2.00 (d, J=10.2Hz, 2H), 1.86 (d, J=10.2Hz, 2H), 1.41 (m, 6H). Mp: 167-169°C ($C_{21}H_{32}N_4O_5S.2H_2O.2CF_3COOH$).

Example 3

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(propylsulfonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using propylsulfonyl chloride instead of methanesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.57 (d, J=8.9Hz, 1H), 7.18 (d, J=2.4Hz, 1H), 6.70 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.80 (broad s), 3.91 (d, J=11.9Hz, 2H), 3.57 (t, J=6.9Hz, 2H), 3.41 (d, J=11.9Hz, 2H), 3.07 (m, 2H), 2.95 (t, J=10.1Hz, 2H), 2.85 (t, J=10.1Hz, 2H), 2.61 (t, J=6.9Hz, 2H), 2.04 (d, J=10.2Hz, 2H), 1.84 (d, J=10.2Hz, 2H), 1.73 (m, 2H), 1.41 (m, 6H), 0.96 (t, J=7.4Hz, 3H). Mp: 113-117°C ($C_{23}H_{36}N_4O_5S.2CF_3COOH.3H_2O$).

Example 4

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(2-propylsulfonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2a, but using isopropylsulfonyl chloride instead of methanesulfonyl chloride, and then hydrolyzing simultaneously the *tert*-butoxycarbonyl and the ethyl ester groups with 5N HCl at 40°C, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.91 (m, 2H), 7.39 (dd, J=8.7Hz, J=2.0Hz, 1H), 4.86 (broad s), 3.79 (d, J=11.9Hz, 2H), 3.62 (t, J=6.9Hz, 2H), 3.55 (d, J=11.9Hz, 2H), 3.42 (m, 3H), 2.99 (t, J=10.1Hz, 2H), 2.64 (t, J=6.9Hz, 2H), 2.00 (m, 4H), 1.56 (m, 6H), 1.33 (d, J=6.8Hz, 6H). Mp: 147-151°C($C_{23}H_{36}N_4O_5S.2HCl$).

Example 5

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(butylsulfonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using butylsulfonyl chloride instead of methanesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.63 (d, J=8.9Hz, 1H), 7.28 (d, J=2.4Hz, 1H), 6.81 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.92 (broad s), 3.88 (d, J=11.9Hz, 2H), 3.58 (t, J=6.9Hz, 2H), 3.41 (d, J=11.9Hz, 2H), 3.11 (m, 2H), 2.95 (t, J=10.1Hz, 4H), 2.61 (t, J=6.9Hz, 2H), 2.04 (d, J=10.2Hz, 2H), 1.84 (d, J=10.2Hz, 2H), 1.66 (m, 2H), 1.41 (m, 8H), 0.85 (t, J=7.4Hz, 3H). Mp: 112-116°C ($C_{24}H_{38}N_4O_5S.2H_2O.2CF_3COOH$).

Example 6

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(*tert*-butylcarbonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using pivaloyl chloride instead of methanesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 8.24 (d, J=2.4Hz, 1H), 7.55 (d, J=8.9Hz, 1H), 6.69 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.80 (broad s), 3.92 (d, J=11.9Hz, 2H), 3.59 (t, J=6.9Hz, 2H), 3.39 (d, J=11.9Hz, 2H), 2.95 (t, J=10.1Hz, 2H), 2.86 (t, J=10.1Hz, 2H), 2.62 (t, J=6.9Hz, 2H), 1.99 (d, J=10.2Hz, 2H), 1.84 (d, J=10.2Hz, 2H), 1.44 (m, 6H), 1.30 (m, 9H). Mp: 31-33°C ($C_{25}H_{38}N_4O_4.2CF_3COOH$).

Example 7

3-[N-[4-(4,4'-Bipiperidin-1-yl)-3-nitrobenzoyl]amino]propionic acid

The compound obtained in reference example 3a was hydrolyzed by treatment with 6N HCl at room temperature overnight to afford the title compound.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 8.33 (m, 1H), 8.02 (m, 1H), 7.45 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.88 (broad s), 3.62 (m, 2H), 3.52 (d, J=11.9Hz, 2H), 3.43 (d, J=11.9Hz, 2H), 3.10 (t, J=10.1Hz, 2H), 2.98 (t, J=10.1Hz, 2H), 2.64 (q, J=6.7Hz, 2H), 2.02 (d, J=10.2Hz, 2H), 1.90 (d, J=10.2Hz, 2H), 1.51 (m, 6H). Mp: 202-204°C

($C_{20}H_{28}N_4O_5.2HCl.H_2O$).

Example 8

3-[N-[4-(4,4'-Bipiperidin-1-yl)-3-(butylsulfonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but starting from the compound obtained in reference example 3 and using butylsulfonyl chloride instead of methanesulfonyl chloride, the title compound was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.87 (s, 1H), 7.69 (m, 1H), 7.57 (m, 1H), 4.86 (broad s), 3.62 (t, J=6.9Hz, 2H), 3.43 (d, J=11.9Hz, 2H), 3.30 (m, 6H), 2.99 (t, J=10.1Hz, 2H), 2.63 (t, J=6.9Hz, 2H), 2.01 (m, 4H), 1.80 (m, 2H), 1.50 (m, 8H), 0.93 (t, J=7.4Hz, 3H). Mp: 75-81°C ($C_{24}H_{38}N_4O_5S.2HCl.4H_2O$).

Example 9

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(methoxycarbonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using methyl chloroformate instead of methanesulfonyl chloride, the title compound was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.78 (d, J=8.9Hz, 1H), 6.82 (dd, J=2.3Hz, J=9.1Hz, 1H), 6.43 (d, J=2.2Hz, 1H), 4.77 (broad s), 4.23 (t, J=6.9Hz, 2H), 4.00 (d, J=11.9Hz, 2H), 3.41 (d, J=11.9Hz, 2H), 3.30 (s, 3H), 2.92 (m, 4H), 2.63 (t, J=6.9Hz, 2H), 2.00 (d, J=10.2Hz, 2H), 1.84 (d, J=10.2Hz, 2H), 1.41 (m, 6H). Mp: 297-298°C ($C_{22}H_{32}N_4O_5.CF_3COOH$).

Example 10

3-[N-[2-(Benzylsulfonylamino)-5-(4,4'-bipiperidin-1-yl)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but starting from the compound obtained in reference example 4 and using benzylsulfonyl chloride instead of methanesulfonyl chloride, the title compound was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.55 (m, 2H), 7.27 (m, 6H), 4.84 (broad s),

4.77 (s, 2H), 3.74 (d, J=11.9Hz, 2H), 3.54 (t, J=6.9Hz, 2H), 3.43 (d, J=11.9Hz, 2H), 3.08 (t, J=10.1Hz, 2H), 2.98 (t, J=10.1Hz, 2H), 2.61 (t, J=6.9Hz, 2H), 2.00 (m, 4H), 1.41 (m, 6H). Mp: 65-67°C ($C_{27}H_{36}N_4O_5S.2CF_3COOH.4H_2O$).

Example 11

3-[N-[2-(Benzylsulfonylamino)-4-(4,4'-bipiperidin-1-yl)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using benzylsulfonyl chloride instead of methanesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.56 (d, J=8.9Hz, 1H), 7.24 (m, 6H), 6.70 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.87 (broad s), 4.44 (s, 2H), 3.84 (d, J=11.9Hz, 2H), 3.48 (t, J=6.9Hz, 2H), 3.41 (d, J=11.9Hz, 2H), 2.95 (t, J=10.1Hz, 2H), 2.86 (t, J=10.1Hz, 2H), 2.56 (t, J=6.9Hz, 2H), 2.00 (d, J=10.1Hz, 2H), 1.86 (d, J=10.1Hz, 2H), 1.41 (m, 8H). Mp: 149-152°C ($C_{27}H_{36}N_4O_5S.2CF_3COOH.2\ H_2O$).

Example 12

4-[N-[2-(Benzylsulfonylamino)-4-(4,4'-bipiperidin-1-yl)benzoyl]amino]butyric acid

a) Ethyl 4-[N-(2-amino-4-fluorobenzoyl)amino]butyrate

Following a similar procedure to that described in reference example 2a, but using ethyl 4-aminobutyrate instead of β-alanine ethyl ester and 2-amino-4-fluorobenzoic acid instead of 4-fluoro-2-nitrobenzoic acid, the desired product was obtained.

b) Ethyl 4-[N-[2-(benzylsulfonylamino)-4-fluorobenzoyl]amino]butyrate

Following a similar procedure to that described in example 2a, but starting from the compound obtained in step a) and using benzylsulfonyl chloride instead of methanesulfonyl chloride, the desired compound was obtained.

c) Title compound

The title compound was obtained by reaction of the compound prepared in step b) with 1-(*tert*-butoxycarbonyl)-4,4'-bipiperidine as described in reference example 2b, followed by hydrolysis of the ethyl ester with 1N NaOH/EtOH and finally of the *tert*-butoxycarbonyl group with trifluoroacetic acid, as described in

preceding examples.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.56 (d, J=8.9Hz, 1H), 7.22 (m, 6H), 6.67 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.81 (broad s), 4.43 (s, 2H), 3.86 (d, J=11.9Hz, 2H), 3.41 (d, J=11.9Hz, 2H), 3.30 (t, J=6.9Hz, 2H), 2.96 (t, J=10.1Hz, 2H), 2.81 (t, J=10.1Hz, 2H), 2.35 (t, J=6.9Hz, 2H), 2.01 (d, J=10.1Hz, 2H), 1.84 (m, 4H), 1.41 (m, 6H). Mp: 71-81°C ($C_{28}H_{38}N_4O_5S.2CF_3COOH$).

Example 13

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-[(4-methoxyphenyl)sulfonylamino]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using 4-methoxybenzenesulfonyl chloride instead of methanesulfonyl chloride, the desired compound was obtained.

^{1}H NMR (300MHz, DMSO-d_6) δ (TMS): 7.66 (d, J=8.9Hz, 2H), 7.51 (d, J=8.9Hz, 1H), 7.01 (d, J=8.9Hz, 2H), 6.84 (d, J=2.3Hz, 1H), 6.54 (dd, J=9.1Hz, J=2.5Hz, 1H), 3.77 (s, 3H), 3.75 (d, J=11.9Hz, 2H), 3.37 (t, J=6.9Hz, 2H), 3.20 (m, 2H), 2.79 (t, J=10.1Hz, 2H), 2.74 (t, J=10.1Hz, 2H), 2.48 (t, J=6.9Hz, 2H), 1.78 (d, J=10.1Hz, 2H), 1.69 (d, J=10.1Hz, 2H), 1.32 (m, 4H), 1.11 (m, 2H). Mp: 245-250°C ($C_{27}H_{36}N_4O_6S.2CF_3COOH.2H_2O$).

Example 14

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(4-tolylsulfonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using toluenesulfonyl chloride instead of methanesulfonyl chloride, the desired compound was obtained.

^{1}H NMR (300MHz, DMSO-d_6) δ (TMS): 7.60 (d, J=8.9Hz, 2H), 7.52 (d, J=8.9Hz, 1H), 7.29 (d, J=8.9Hz, 2H), 6.82 (d, J=2.3Hz, 1H), 6.54 (dd, J=9.1Hz, J=2.5Hz, 1H), 3.74 (d, J=11.9Hz, 2H), 3.37 (t, J=6.9Hz, 2H), 3.30 (m, 2H), 2.79 (t, J=10.1Hz, 2H), 2.71 (t, J=10.1Hz, 2H), 2.47 (t, J=6.9Hz, 2H), 2.29 (s, 3H), 1.76 (d, J=10.1Hz, 2H), 1.67 (d, J=10.1Hz, 2H), 1.29 (m, 4H), 1.05 (m, 2H). Mp: 264-272°C ($C_{27}H_{36}N_4O_5S.2CF_3COOH.3H_2O$).

Example 15

3-[N-[2-[4-(Acetylamino)phenylsulfonylamino]-4-(4,4'-bipiperidin-1-yl)-benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using 4-acetamidobenzenesulfonyl chloride instead of methanesulfonyl chloride, the desired compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.66 (s, 4H), 7.40 (d, J=8.9Hz, 1H), 7.05 (d, J=2.3Hz, 1H), 6.61 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.86 (broad s), 3.90 (d, J=11.9Hz, 2H), 3.50 (t, J=6.9Hz, 2H), 3.43 (d, J=11.9Hz, 2H), 2.98 (t, J=10.1Hz, 2H), 2.84 (t, J=10.1Hz, 2H), 2.55 (t, J=6.9Hz, 2H), 2.13 (s, 3H), 2.01 (d, J=10.1Hz, 2H), 1.80 (d, J=10.1Hz, 2H), 1.46 (m, 4H), 1.28 (m, 2H). Mp: 226-229 °C ($C_{28}H_{37}N_5O_6S.2CF_3COOH$).

Example 16

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-[(3-pyridylacetyl)amino]benzoyl]amino]propionic acid

a) **Ethyl 3-[N-[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]-2-[(3-pyridylacetyl)amino]benzoyl]amino]propionate**

To a solution of 3-pyridylacetic acid hydrochloride (0.2 g, 1.19 mmol) in anhydrous DMF (20 mL), cooled in an ice bath, was added NEt_3 (0.18 mL) and the mixture was stirred at room temperature for 10 min. Next, the compound obtained in reference example 2 (0.6 g, 1.19 mmol) and 1-hydroxybenzotriazole (0.17 g) were added. The resulting mixture was placed again in an ice bath and finally dicyclohexylcarbodiimide (0.24 g) was added. The mixture was removed from the ice bath and was stirred at room temperature for 48 h. The insoluble material was filtered off and DMF was removed. The resulting crude product was partitioned between $CHCl_3$ and 0.5N NaOH, and was extracted 3x with $CHCl_3$. The combined organic extracts were dried and concentrated to afford 1.2 g of a crude product. This was purified by chromatography on silica gel ($CHCl_3$-MeOH, 2%), yielding 0.62 g of the desired compound (84%).

b) Title compound

The compound obtained in step a) was treated first with 1N NaOH/EtOH and then with trifluoroacetic acid as described in preceding examples, to afford the title compound.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 8.80 (d, J=1.8Hz, 1H), 8.73 (dd, J=5.5Hz, J=1.2Hz, 1H), 8.39 (dt, J=7.9Hz, J=1.7Hz, 1H), 7.99 (d, J=9.1Hz, 1H), 7.91 (dd, J=8.0Hz, J=5.5Hz, 1H), 7.17 (dd, J=9.1Hz, J=2.4Hz, 1H), 6.77 (d, J=2.2Hz, 1H), 4.86 (broad s), 4.60 (s, 2H),), 4.39 (t, J=6.9Hz, 2H), 4.00 (d, J=11.9Hz, 2H), 3.42 (d, J=11.9Hz, 2H), 2.91 (m, 6H), 2.00 (d, J=10.1Hz, 2H), 1.86 (d, J=10.1Hz, 2H), 1.37 (m, 6H). Mp: 130-132 °C ($C_{27}H_{35}N_5O_4.2CF_3COOH$).

Example 17

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(styrylsulfonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using trans-β-styrenesulfonyl chloride instead of methanesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.45 (m, 7H), 7.04 (m, 2H), 6.62 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.83 (broad s), 3.89 (d, J=11.9Hz, 2H), 3.55 (t, J=6.9Hz, 2H), 3.38 (d, J=11.9Hz, 2H), 2.89 (t, J=10.1Hz, 2H), 2.80 (t, J=10.1Hz, 2H), 2.56 (t, J=6.9Hz, 2H), 1.90 (d, J=10.1Hz, 2H), 1.76 (d, J=10.1Hz, 2H), 1.30 (m, 6H). Mp: 267-268 °C ($C_{28}H_{36}N_4O_5S.CF_3COOH$).

Example 18

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-(2-naphthylsulfonylamino)benzoyl]amino]propionic acid

Following a similar procedure to that described in example 2, but using 2-naphthalenesulfonyl chloride instead of methanesulfonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 8.35 (s, 1H), 7.93 (m, 3H), 7.64 (m, 3H), 7.32 (d, J=8.9Hz, 1H), 7.06 (d, J=2.4Hz, 1H), 6.54 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.83 (broad s), 3.85 (d, J=11.9Hz, 2H), 3.42 (t, J=6.9Hz, 2H), 3.40 (d, J=11.9Hz, 2H), 2.93 (t, J=10.1Hz, 2H), 2.77 (t, J=10.1Hz, 2H), 2.46 (t, J=6.9Hz, 2H), 1.92 (d, J=10.1Hz, 2H), 1.76 (d, J=10.1Hz, 2H), 1.40 (m, 4H), 1.19 (m, 2H). Mp: 276-279°C ($C_{30}H_{36}N_4O_5S.CF_3COOH$).

Example 19

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-[(1-phenyl-1-cyclopropanecarbonyl)amino]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 16, but using 1-phenyl-1-cyclopropanecarboxylic acid instead of 3-pyridylacetic acid, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 8.15 (d, J=2.4Hz, 1H), 7.40 (m, 6H), 6.64 (dd, J=9.1Hz, J=2.5Hz, 1H), 4.83 (broad s), 3.87 (d, J=11.9Hz, 2H), 3.45 (d, J=11.9Hz, 2H),), 3.35 (t, J=6.9Hz, 2H), 2.95 (t, J=10.1Hz, 2H), 2.83 (t, J=10.1Hz, 2H), 2.47 (t, J=6.9Hz, 2H), 2.00 (d, J=10.1Hz, 2H), 1.83 (d, J=10.1Hz, 2H), 1.58 (m, 2H), 1.40 (m, 6H), 1.17 (m, 2H). Mp: 159-166 °C ($C_{30}H_{38}N_4O_4.2CF_3COOH.H_2O$).

Example 20

3-[N-[4-(4,4'-Bipiperidin-1-yl)benzoyl]amino]-2-methylpropionic acid

a) Methyl 3-[N-[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoyl]amino]-2-methylpropionate

The compound obtained in reference example 1 (0.5 g, 12.8 mmol) was placed in anhydrous DMF (10 mL) and the mixture was heated at 60°C for 2 h to obtain dissolution of the product. To this solution was then added methyl 3-amino-2-methylpropionate hydrochloride (0.196 g, 12.8 mmol) and 1-hydroxybenzotriazole (0.17 g). Next, NEt_3 (0.17 mL) was addded and finally dicyclohexylcarbodiimide (0.25 g). The reaction mixture was stirred at room temperature overnight. The insoluble material was filtered off and DMF was removed. The resulting crude product was partitioned between $CHCl_3$ and 1N NaOH, and was extracted 3x with $CHCl_3$. The combined organic extracts were dried and concentrated to afford 0.6 g of a crude product. This was purified by chromatography on silica gel (EtOAc-Hex, 9:1), yielding 0.31 g of the desired compound (50%).

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 5N HCl at room temperature for 24 h to give the title compound.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.70 (d, J=8.9Hz, 2H), 7.02 (d, J=8.9Hz, 2H), 4.70 (broad m), 3.85 (d, J=11.9Hz, 2H), 3.44 (m, 4H), 2.91 (t, J=10.1Hz, 2H), 2.73 (t, J=10.1Hz, 2H), 2.59 (m, 1H), 1.97 (d, J=10.2Hz, 2H), 1.82 (d, J=10.2Hz, 2H), 1.41 (m,

6H), 1.13 (d, J=7.0Hz, 3H). Mp: 251-255 °C ($C_{21}H_{31}N_3O_3.1.5H_2O$).

Example 21

3-[N-[4-(4,4'-Bipiperidin-1-yl)benzoyl]amino]-3-methylpropionic acid

Following a similar procedure to that described in example 20, but using ethyl 3-aminobutyrate instead of methyl 3-amino-2-methyl propionate, the title compound was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 8.01 (d, J=8.9Hz, 2H), 7.94 (d, J=8.9Hz, 2H), 5.05 (broad m), 4.49 (m, 1H), 3.73 (m, 4H), 3.33 (m, 2H), 2.99 (t, J=10.1Hz, 2H), 2.62 (m, 2H), 2.1-1.4 (m, 10H), 1.38 (m, 3H). Mp: 161-170 °C ($C_{21}H_{31}N_3O_3.2HCl.1.5H_2O$).

Example 22

3-[N-[4-(4,4'-Bipiperidin-1-yl)benzoyl]amino]-2(*S*)-[(2-thienylcarbonyl)amino]propionic acid

a) Methyl 3-amino-2(*S*)-[(2-thienylcarbonyl)amino]propionate

To a solution of 3-amino-2(*S*)-[(benzyloxycarbonyl)amino]propionic acid (5 g, 21 mmol) in MeOH (60 mL), cooled to -20°C, was added dropwise $SOCl_2$ (1.67 mL, 23 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was evaporated to dryness and the residue was treated with aqueous saturated Na_2CO_3 solution and extracted with $CHCl_3$ (3x). The combined organic extracts were dried and concentrated, yielding 5.1 g of methyl 3-amino-2(*S*)-[(benzyloxycarbonyl)amino]propionate.

This product (5.1 g, 20 mmol) was dissolved in anhydrous THF (40 mL) and to this solution, cooled in an ice bath, was added BOC_2O (3.9 g, 18 mmol) and NEt_3 (2.62 mL). The reaction mixture was stirred at room temperature overnight. The resulting solution was concentrated to half the initial volume and was then washed 2x with 1% citric acid solution and with EtOAc. The organic phase was washed with 1% aqueous $NaHCO_3$ solution, dried and concentrated to give 6.1 g of methyl 2(*S*)-[(benzyloxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)amino]propionate. This compound was then hydrogenated following a similar procedure to that described in reference example 2c, to give methyl 2(*S*)-amino-3-[(*tert*-butoxycarbonyl)amino]propionate (2.75 g).

This compound (0.6 g, 2.7 mmol) was then dissolved in CH_2Cl_2 (10 mL)

and NEt_3 (0.37 mL), and to the resulting solution, cooled in an ice bath, was added dropwise 2-thienylcarbonyl chloride (0.28 mL, 2.7 mmol). The reaction mixture was stirred at room temperature overnight. H_2O was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2x) and the combined organic extracts were dried and concentrated. The resulting residue (1.04 g) was purified by chromatography on silica gel (EtOAc-Hex, 80%) to give 0.69 g of methyl 3-[(*tert*-butoxycarbonyl)amino]-2(*S*)-[(2-thienylcarbonyl)amino]propionate.

To a solution of this compound (0.69 g, 2.1 mmol) in MeOH (5 mL) was added dropwise and at 0°C a 7% HCl/dioxane solution. The mixture was stirred at room temperature overnight and was then evaporated to dryness. The resulting residue was treated with hot EtOAc and upon removal of the solvent, 0.48 g of the desired compound was obtained.

b) Methyl 3-[N-[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoyl]amino]-2(*S*)-[(2-thienylcarbonyl)amino]propionate

Following a similar procedure to that described in example 20a, but using the compound obtained in step a) above instead of methyl 3-amino-2-methylpropionate, the desired compound was obtained.

c) Title compound

The title compound was obtained by hydrolysis of the compound obtained in step b) with 1N NaOH in MeOH first at 40°C for 18 h and then at room temperature for further 18 h, and subsequent removal of the *tert*-butoxycarbonyl group by treatment with trifluoroacetic acid as described in preceding examples.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.77 (m, 3H), 7.70 (dd, J=1.0Hz, J=5.0Hz, 1H), 7.17 (t, J=3.7Hz, 2H), 7.11 (d, J=8.9Hz, 2H), 4.88 (broad s), 4.82 (m, 1H), 3.92 (m, 4H), 3.45 (d, J=12.4Hz, 2H), 2.99 (m, 4H), 2.03 (d, J=9.2Hz, 2H), 1.92 (d, J=9.2Hz, 2H), 1.48 (m, 6H).

Example 23

3-[N-[4-(4,4'-Bipiperidin-1-yl)benzoyl]amino]-3-phenylpropionic acid

Following a similar procedure to that described in example 20, but using ethyl 3-amino-3-phenylpropionate instead of methyl 3-amino-2-

methylpropionate, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 8.04 (d, J=8.4Hz, 2H), 7.88 (d, J=8.4Hz, 2H), 7.42 (m, 5H), 5.60 (m, 1H), 4.83 (broad s), 3.75 (m, 4H), 3.47 (d, J=12.4Hz, 2H), 3.03 (m, 4H), 2.1-1.2 (m, 10H). Mp: 156-164 °C ($C_{26}H_{33}N_3O_3.2HCl.1.5H_2O$).

Example 24

3-[N-[4-(4,4'-Bipiperidin-1-yl)benzoyl]amino]-2(*S*)-(phenylsulfonylamino)propionic acid

Following a similar procedure to that described in example 20, but using methyl 3-amino-2(*S*)-(phenylsulfonylamino)propionate (obtained in reference example 5) instead of methyl 3-amino-2-methylpropionate, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.97 (m, 2H), 7.83 (m, 4H), 7.47 (m, 3H), 4.79 (broad s), 4.23 (m, 1H), 3.76 (m, 4H), 3.49 (m, 4H), 2.99 (m, 2H), 2.1-1.2 (m, 10H). Mp: 220-221 °C ($C_{26}H_{34}N_4O_5S.2HCl.2H_2O$).

Example 25

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-trifluoromethylbenzoyl]amino]propionic acid

a) *Tert*-butyl 3-[N-(4-fluoro-2-trifluoromethylbenzoyl)amino]propionate

To a solution of 4-fluoro-2-trifluoromethylbenzoyl chloride (0.6 g, 2.6 mmol) in $CHCl_3$ (15 mL) was added β-alanine *tert*-butyl ester hydrochloride (0.48 g, 2.6 mmol). Next, the mixture was cooled in an ice bath and NEt_3 (0.72 mL) was slowly added. When the addition was complete, the reaction mixture was stirred at room temperature overnight. Then, 1N NaOH was added and the aqueous phase was extracted with $CHCl_3$ (3x). The combined organic extracts were dried and concentrated to afford 1.07 g of the desired product.

b) *Tert*-butyl 3-[N-[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]-2-trifluoromethylbenzoyl]amino]propionate

Following a similar procedure to that described in reference example 2b, but starting from the compound obtained in step a) above, and purifying the resulting crude product by chromatography on silica gel (CH_2Cl_2-MeOH, 1%), 0.24 g of the desired compound was obtained.

c) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step b) above, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.35 (d, J=8.9Hz, 1H), 7.15 (m, 2H), 4.84 (broad s), 3.88 (d, J=11.9Hz, 2H), 3.56 (t, J=6.9Hz, 2H), 3.40 (d, J=11.9Hz, 2H), 2.95 (t, J=10.1Hz, 2H), 2.79 (t, J=10.1Hz, 2H), 2.60 (t, J=6.9Hz, 2H), 1.99 (d, J=10.2Hz, 2H), 1.85 (d, J=10.2Hz, 2H), 1.41 (m, 6H). Mp: 191-195 °C ($C_{21}H_{28}F_3N_3O_3$. CF_3COOH).

Example 26

3-[N-[4-(4,4'-Bipiperidin-1-yl)-2-fluorobenzoyl]amino]propionic acid

Following a similar procedure to that described in example 25, but using 2,4-difluorobenzoyl chloride instead of 4-fluoro-2-trifluoromethylbenzoyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.69 (t, J=9.1Hz, 1H), 6.77 (dd, J=8.9Hz, J=2.3Hz, 1H), 6.63 (dd, J=15.9Hz, J=2.3Hz, 1H), 4.82 (broad s), 3.92 (d, J=11.9Hz, 2H), 3.61 (t, J=6.9Hz, 2H), 3.40 (d, J=11.9Hz, 2H), 2.94 (t, J=10.1Hz, 2H), 2.81 (t, J=10.1Hz, 2H), 2.60 (t, J=6.9Hz, 2H), 2.00 (d, J=10.2Hz, 2H), 1.82 (d, J=10.2Hz, 2H), 1.41 (m, 6H). Mp: 239-240 °C ($C_{20}H_{28}FN_3O_3.CF_3COOH$).

Example 27

3-[N-[6-(4,4'-Bipiperidin-1-yl)nicotinoyl]amino]propionic acid

a) *Tert*-butyl 3-[N-[6-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]nicotinoyl]amino]propionate

Following a similar procedure to that described in reference example 2 (steps a and b), but starting from 6-chloronicotinic acid and β-alanine *tert*-butyl ester, the desired product was obtained.

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 5N HCl at room temperature for 48 h to give the title compound.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 8.34 (m, 2H), 7.45 (d, J=9.6Hz, 1H), 4.86 (broad s), 4.30 (d, J=11.9Hz, 2H), 3.62 (t, J=6.9Hz, 2H), 3.42 (d, J=11.9Hz, 2H), 3.31 (t, J=10.1Hz, 2H), 2.97 (t, J=10.1Hz, 2H), 2.63 (t, J=6.9Hz, 2H), 2.00 (d, J=10.2Hz,

4H), 1.41 (m, 6H). Mp: 246-247 °C ($C_{19}H_{28}N_4O_3.2HCl.H_2O$).

Example 28

3-[N-[6-(4,4'-Bipiperidin-1-yl)nicotinoyl]amino]-3-methylpropionic acid

a) 6-[1'-(*Tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]nicotinic acid

Following a similar procedure to that described in reference example 2b, but starting from methyl 6-chloronicotinate and hydrolyzing the resulting methyl ester with KOH in MeOH-H_2O at reflux, the desired compound was obtained.

^1H NMR (300MHz, $DMSO_{d6}$) δ (TMS): 8.77 (s, 1H), 8.07 (d, J=8.8Hz, 1H). 6.92 (d, J=8.8Hz, 1H), 4.61 (d, J=10.5Hz, 2H), 4.17 (d, J=10.5Hz, 2H), 3.60 (s ancha), 2.97 (t, J=11.5Hz, 2H), 2.81 (m, 2H), 1.90 (m, 4H), 1.57 (s, 9H), 1.28 (m, 8H).

b) Ethyl 3-[N-[6-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]nicotinoyl]amino]-3-methylpropionate

To a mixture of the compound obtained in step a) (2 g, 5.27 mmol) and N-hydroxysuccinimide (0.66 g, 5.7 mmol) in $CHCl_3$ (27 mL), cooled in an ice bath, was added dicyclohexylcarbodiimide (1.18 g) and the reatcion mixture was stirred at room temperature overnight. The insoluble material was filtered off and the filtrate was evaporated to dryness, yielding 3.2 g of a crude product.

To a solution of this crude product (0.69 g, 1.23 mmol) in CH_2Cl_2 (15 mL) was added ethyl 3-aminobutyrate (0.18 mL, 1.23 mmol). The reaction mixture was stirred at room temperature overnight. Then, H_2O was added and was extracted with CH_2Cl_2 (3x). The combined organic extracts were dried and concentrated to give 0.7 g of a crude product that was purified by chromatography on silica gel (EtOAc), yielding 0.4 g of the desired product.

c) Title compound

The compound obtained in step b) was hydrolyzed by treatment with 5N HCl at room temperature overnight to afford the title compound.

^1H NMR (300MHz, CD_3OD) δ (TMS): 8.33 (m, 3H), 7.43 (m, 1H), 4.77 (broad s), 4.47 (m, 1H), 4.31 (m, 2H), 3.41(m, 4H), 2.97 (m, 2H), 2.59 (m, 4H), 2.1-1.1 (m, 10H). Mp: 191-197 °C ($C_{20}H_{30}N_4O_3.2HCl.1.5H_2O$).

Example 29

3-[N-[[4-(4,4'-Bipiperidin-1-yl)phenyl]sulfonyl]amino]propionic acid

a) *Tert*-butyl 3-[N-[(4-fluorophenyl)sulfonyl]amino]propionate

To a solution of 4-fluorobenzenesulfonyl chloride (0.75 g, 3.85 mmol) in CH_2Cl_2 (10 mL) was added β-alanine *tert*-butyl ester hydrochloride (0.7 g, 3.85 mmol). The resulting solution was cooled to 0°C, NEt_3 (1.18 mL) was added and the reaction mixture was stirred at room temperature overnight. The resulting mixture was poured into aqueous $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to afford 1.05 g of a crude product that was directly used in the next step as obtained.

b) *Tert*-butyl 3-[N-[[4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]phenyl]sulfonyl]amino]propionate

Following a similar procedure to that described in reference example 2b, but starting from the compound obtained in step a) above, the desired compound was obtained (0.58 g, 53%).

c) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step b) above, the title compound was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.63 (d, J=8.9Hz, 2H), 7.01 (d, J=8.9Hz, 2H), 4.82 (broad s), 3.96 (d, J=11.9Hz, 2H), 3.40 (d, J=11.9Hz, 2H), 3.04 (t, J=6.9Hz, 2H), 2.95 (t, J=10.1Hz, 2H), 2.82 (t, J=10.1Hz, 2H), 2.43 (t, J=6.9Hz, 2H), 2.00 (d, J=10.2Hz, 2H), 1.84 (d, J=10.2Hz, 2H), 1.41 (m, 6 H). Mp: 125-131 °C ($C_{19}H_{29}N_3O_4S.CF_3COOH.H_2O$).

Example 30

3-[N-[4-[4-(4-Piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) *Tert*-butyl 3-[N-(4-fluorobenzoyl)amino]propionate

To a solution of 4-fluorobenzoyl chloride (3.3 mL, 27.5 mmol) and β-alanine *tert*-butyl ester hydrochloride (5 g, 27.5 mmol) in CH_2Cl_2 (40 mL), cooled in an ice bath, was slowly added NEt_3 (3.83 mL). When the addition was complete, the reaction mixture was stirred at room temperature overnight. More NEt_3 (3.83 mL) was added and the mixture was then refluxed for 4 h. The

resulting mixture was treated with saturated $NaHCO_3$ solution and was extracted with CH_2Cl_2 (3x). The combined organic extracts were dried and concentrated to afford 7.38 g of a crude product that was directly used in the next step as obtained.

b) *Tert*-butyl 3-[N-[4-(piperazinyl)benzoyl]amino]propionate

To a solution of the product obtained in step a) (2 g, 7.5 mmol) in anhydrous DMSO (30 mL) and diisopropylethylamine (1.33 mL), was added piperazine (2.6 g, 30 mmol) and the reaction mixture was heated at 130°C for 48 h. DMSO was removed, and the resulting residue was partitioned between 1N NaOH and $CHCl_3$, and was extracted with $CHCl_3$ (3x). The combined organic extracts were dried and concentrated to afford a crude product that was purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3, 60:8:0.2). 1.7 g of the desired product was obtained (68%).

c) *Tert*-butyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]propionate

To a solution of the compound obtained in step b) (0.5 g, 1.5 mmol) and 1-(*tert*-butoxycarbonyl)piperidin-4-one (0.3 g, 1.5 mmol) in anhydrous THF (15 mL) was added acetic acid (0.85 mL). Next, sodium triacetoxyborohydride (0.4 g, 1.8 mmol) was added in portions, and the reaction mixture was stirred at room temperature overnight. The resulting solution was evaporated to dryness and the residue was partitioned between saturated Na_2CO_3 solution and EtOAc. The aqueous phase was extracted two more times with EtOAc and the combined organic extracts were dried and concentrated to give 0.8 g of a crude product. This was purified by chromatography on silica gel ($CHCl_3$-MeOH, 3%), yielding 0.522 g of the desired compound (88%).

d) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step c), the title compound was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.76 (d, J=8.9Hz, 2H), 7.01 (d, J=8.9Hz, 2H), 4.87 (broad s), 3.49 (m, 6H), 3.33 (m, 2H), 3.10 (m, 4H), 2.63 (t, J=6.9Hz, 2H), 2.40 (d, J=10.2Hz, 2H), 2.3-1.7 (m, 5H). Mp: 215-223 °C ($C_{19}H_{28}N_4O_3.3CF_3COOH$).

Example 31

3-Methyl-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) Ethyl 4-(piperazinyl)benzoate

Following a similar procedure to that described in example 30b, but starting from ethyl 4-fluorobenzoate, the desired compound was obtained.

b) Ethyl 4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoate

Following a similar procedure to that described in example 30c, but starting from the compound obtained in step a), the desired compound was obtained.

c) 4-[4-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoic acid

Following the hydrolysis procedure described in reference example 1b, but heating at reflux overnight, the desired compound was obtained.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 7.94 (d, J=8.8Hz, 2H), 6.85 (d, J=8.8Hz, 2H), 5.5 (COOH), 4.17 (m, 2H), 3.38 (m, 4H), 2.72 (m, 6H), 2.52 (m, 1H), 1.85 (d, J=10.5Hz, 2H), 1.52 (m, 2H), 1.45 (s, 9H).

d) Ethyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]-3-methylpropionate

Following a similar procedure to that described in reference example 2a, but starting from the compound obtained in step c) and using ethyl 3-aminobutyrate instead of β-alanine ethyl ester, the desired compound was obtained.

e) Title compound

The title compound was obtained from the compound obtained in step d) by hydrolysis of the ethyl ester with 1N NaOH in EtOH followed by removal of the *tert*-butoxycarbonyl group with trifluoroacetic acid as described in preceding examples.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.77 (d, J=8.9Hz, 2H), 7.03 (d, J=8.9Hz, 2H), 4.78 (s), 4.48 (m, 1H), 3.56 (m, 11H), 3.10 (t, J=11.8Hz, 2H), 2.58 (AB system, J= 13Hz, J=6.5Hz, 2H), 2.49 (d, J=10.2Hz, 2H), 2.00 (m, 2H), 1.29 (d, J=7.8Hz, 3H). Mp: 207-209 °C ($C_{20}H_{30}N_4O_3.2CF_3COOH.H_2O$).

Example 32

2-Methyl-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 31, but using methyl 3-amino-2-methylpropionate instead of ethyl 3-aminobutyrate, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.77 (d, J=8.9Hz, 2H), 7.05 (d, J=8.9Hz, 2H), 4.84 (s), 3.56 (m, 13H), 3.10 (t, J=11.8Hz, 2H), 2.80 (m, 1H), 2.43 (d, J=10.2Hz, 2H), 1.99 (m, 2H), 1.20 (d, J=7.8Hz, 3H). Mp: 193-196 °C ($C_{20}H_{30}N_4O_3.2CF_3COOH.H_2O$).

Example 33

3-Phenyl-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) Ethyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]-3-phenylpropionate

Following a similar procedure to that described in example 31d, but using ethyl 3-amino-3-phenylpropionate instead of ethyl 3-aminobutyrate, the desired compound was obtained.

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 5N HCl to give the title compound.

^{1}H NMR (300MHz, CD_3OD+DMSO-d_6) δ (TMS): 7.81 (d, J=8.9Hz, 2H), 7.36 (m, 5H), 7.03 (d, J=8.9Hz, 2H), 5.58 (m, 1H), 4.61 (s), 3.48 (m, 2H), 3.40 (m, 4H), 2.99 (t, J=11.8Hz, 2H), 2.94 (m, 2H), 2.84 (m, 4H), 2.17 (d, J=10.2Hz, 2H), 1.84 (m, 3H). Mp: 172-179 °C ($C_{25}H_{32}N_4O_3.3.5H_2O$).

Example 34

3-[N-[6-[4-(4-Piperidinyl)piperazin-1-yl]nicotinoyl]amino]propionic acid

a) Methyl 6-(piperazinyl)nicotinate

Following a similar procedure to that described in example 30b, but starting from methyl 6-chloronicotinate, the desired compound was obtained.

b) Methyl 6-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]nicotinate

Following a similar procedure to that described in example 30c, but starting from the compound obtained in step a), the desired compound was obtained.

c) 6-[4-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]nicotinic acid

Following the hydrolysis procedure described in reference example 1b, but using MeOH instead of EtOH, the desired compound was obtained.

^{1}H NMR (300MHz, CD_3OD δ (TMS): 8.70 (s, 1H), 8.04 (dd, J=8.8Hz, J=2.3Hz, 1H), 6.80 (d, J=8.8Hz, 1H), 4.7 (COOH), 4.14 (m, 2H), 3.65 (m, 4H), 2.80 (m, 6H), 2.61 (m, 1H), 1.94 (d, J=10.5Hz, 2H), 1.45 (s, 9H), 1.44 (m, 2H).

d) *Tert*-butyl 3-[N-[6-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]nicotinoyl]amino]propionate

Following a similar procedure to that described in reference example 2a, but using the compound obtained in step c) instead of 4-fluoro-2-nitrobenzoic acid, the desired compound was obtained.

e) Title compound

The compound obtained in step d) was hydrolyzed by treatment with 6N HCl at room temperature overnight to give the title compound.

^{1}H NMR (300MHz, CD_3OD+D_2O) δ (TMS): 8.54 (d, J=2.1Hz, 1H), 8.16 (dt, J=9.1Hz, J=3.3Hz, 1H), 7.13 (d, J=9.1Hz, 1H), 4.69 (s), 4.06 (m, 4H), 3.56 (m, 9H), 3.15 (t, J=11.8Hz, 2H), 2.64 (m, 2H), 2.49 (d, J=10.2Hz, 2H), 2.12 (m, 2H) Mp: 274-279 °C ($C_{18}H_{27}N_5O_3.3HCl.0.5H_2O$).

Example 35

3-Methyl-3-[N-[6-[4-(4-piperidinyl)piperazin-1-yl]nicotinoyl]amino]propionic acid

Following a similar procedure to that described in example 34, but using ethyl 3-aminobutyrate instead of β-alanine *tert*-butyl ester, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD+D_2O) δ (TMS): 8.56 (d, J=2.1Hz, 1H), 8.16 (dt, J=9.1Hz, J=3.3Hz, 1H), 7.13 (d, J=9.1Hz, 1H), 4.73 (s), 4.46 (m, 1H), 4.06 (m, 4H), 3.56 (m, 7H), 3.15 (t, J=11.8Hz, 2H), 2.64 (m, 2H), 2.49 (d, J=10.2Hz, 2H), 2.12 (m, 2H), 1.29 (d, J=7.8Hz, 3H) Mp: 263-269 °C ($C_{19}H_{29}N_5O_3.3HCl$).

Example 36

3-[N-[4-[4-(4-Piperidinyl)piperazin-1-yl]-2-trifluoromethylbenzoyl]amino]propionic acid

a) *Tert*-butyl 3-[N-[4-(piperazinyl)-2-trifluoromethylbenzoyl]amino]propionate

Following a similar procedure to that described in example 30b, but starting from the compound obtained in example 25a, the desired compound was obtained.

b) *Tert*-butyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]-2-trifluoromethylbenzoyl]amino]propionate

Following a similar procedure to that described in example 30c, but starting from the compound obtained in step a), the desired compound was obtained.

c) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step b), the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.43 (d, J=8.9Hz, 1H), 7.30 (s, 1H), 7.23 (d, J=8.9Hz, 1H), 4.83 (broad s), 3.55 (m, 11H), 3.30 (m, 2H), 3.12 (t, J=11.8Hz, 2H), 2.60 (t, J=6.9Hz, 2H), 2.46 (d, J=10.2Hz, 2H), 2.12 (m, 2H). Mp: 168-171 °C ($C_{20}H_{27}F_3N_4O_3.3CF_3COOH.H_2O$).

Example 37

3-[N-[2-Methyl-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) Ethyl 2-methyl-4-(piperazinyl)benzoate

Following a similar procedure to that described in example 30b, but starting from ethyl 4-bromo-2-methylbenzoate, the desired compound was obtained.

b) Ethyl 4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]-2-methylbenzoate

Following a similar procedure to that described in example 30c, but starting from the compound obtained in step a), the desired compound was obtained.

c) 4-[4-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]-2-methylbenzoic acid

The compound obtained in step b) was hydrolyzed by treatment with 2N NaOH in EtOH at reflux for 2 days to give the desired product.

d) *Tert*-butyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]-2-

methylbenzoyl]amino]propionate

Following a similar procedure to that described in reference example 2a, but starting from the compound obtained in step c) and using the *tert*-butyl ester of β-alanine instead of its ethyl ester, the desired compound was obtained.

e) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step d), the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.33 (d, J=8.9Hz, 1H), 6.85 (m, 2H), 4.84 (broad s), 3.55 (m, 13H), 3.13 (t, J=11.8Hz, 2H), 2.63 (t, J=6.9Hz, 2H), 2.49 (d, J=10.2Hz, 2H), 2.41 (s, 3H), 2.05 (m, 2H). Mp: 126-134 °C ($C_{20}H_{30}N_4O_3.3CF_3COOH$).

Example 38

3-[N-[[4-[4-(4-Piperidinyl)piperazin-1-yl]phenyl]sulfonyl]amino]propionic acid

a) *Tert*-butyl 3-[N-[[4-(piperazinyl)phenyl]sulfonyl]amino]propionate

Following a similar procedure to that described in example 30b, but starting from the compound obtained in example 29a, the desired compound was obtained.

b) *Tert*-butyl 3-[N-[[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]sulfonyl]amino]propionate

Following a similar procedure to that described in example 30c, but starting from the compound obtained in step a), the desired compound was obtained.

c) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step b), the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.80 (d, J=8.9Hz, 2H), 7.17 (d, J=8.9Hz, 2H), 4.86 (broad s), 3.60 (m, 10H), 3.15 (m, 4H), 2.41 (s, 4H), 2.10 (m, 3H). Mp: 208-209 °C ($C_{18}H_{28}N_4O_4S.3CF_3COOH$).

Example 39

3-[N-[2-Chloro-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 37, but

starting from ethyl 2-chloro-4-fluorobenzoate instead of ethyl 4-bromo-2-methylbenzoate, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.43 (d, J=8.5Hz, 1H), 7.09 (d, J=2.4Hz, 1H), 7.00 (dd, J=8.6Hz, J=2.4Hz, 1H), 4.82 (broad s), 3.53 (m, 13H), 3.13 (t, J=11.8Hz, 2H), 2.64 (t, J=6.9Hz, 2H), 2.47 (d, J=10.2Hz, 2H), 2.00 (m, 2H). Mp: 45-55 °C ($C_{19}H_{27}ClN_4O_3.2CF_3COOH.2H_2O$).

Example 40

3-[N-[2-Fluoro-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) Ethyl 4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]-2-fluorobenzoate

Following a similar procedure to that described in example 30b, but starting from ethyl 2,4,-difluorobenzoate and using 1-(*tert*-butoxycarbonyl)piperazine instead of piperazine, the desired compound was obtained.

b) Ethyl 2-fluoro-4-(piperazinyl)benzoate

The compound obtained in step a) above was deprotected with trifluoroacetic acid in CH_2Cl_2 following a similar procedure to that described in example 1b, to give the desired compound.

c) Ethyl 4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]-2-fluorobenzoate

Following a similar procedure to that described in example 30c, but starting from the compound obtained in step b), the desired compound was obtained.

d) 4-[4-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]-2-fluorobenzoic acid

The compound obtained in step c) was hydrolyzed by treatment with 1N NaOH in EtOH at room temperature overnight to give the title compound.

e) *Tert*-butyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]-2-fluorobenzoyl]amino]propionate

Following a similar procedure to that described in reference example 2a, but starting from the compound obtained in step d) and using the *tert*-butyl ester of β-alanine instead of its ethyl ester, the desired compound was obtained.

f) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step e), the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.77 (t, J=9.1Hz, 1H), 6.90 (dd, J=8.9Hz, J=2.4Hz, 1H), 6.83 (dd, J=15.9Hz, J=2.4Hz, 1H), 4.88 (broad s), 3.53 (m, 13H), 3.12 (t, J=11.8Hz, 2H), 2.63 (t, J=6.9Hz, 2H), 2.46 (d, J=10.2Hz, 2H), 2.00 (m, 2H). Mp: 187-191°C ($C_{19}H_{27}FN_4O_3.2CF_3COOH.H_2O$).

Example 41

3-Phenyl-3-[N-[6-[4-(4-piperidinyl)piperazin-1-yl]nicotinoyl]amino]propionic acid

Following a similar procedure to that described in example 34, but using ethyl 3-amino-3-phenylpropionate instead of β-alanine *tert*-butyl ester, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD+D_2O) δ (TMS): 8.57 (d, J=2.1Hz, 1H), 8.30 (dd, J=9.3Hz, J=2.3Hz, 1H), 7.37 (m, 6H), 5.54 (t, J=7.8Hz, 1H), 4.84 (s), 4.12 (m, 4H), 3.64 (m, 7H), 3.18 (t, J=11.8Hz, 2H), 3.06 (m, 2H), 2.52 (d, J=10.2Hz, 2H), 2.12 (m, 2H). Mp: 227-233°C ($C_{24}H_{31}N_5O_3.2HCl.4H_2O$).

Example 42

3-[N-[2-Fluoro-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-3-phenylpropionic acid

Following a similar procedure to that described in example 40, but using ethyl 3-amino-3-phenylpropionate instead of β-alanine *tert*-butyl ester, and carrying out the final hydrolysis with 6N HCl at room temperature overnight, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.72 (t, J=8.6Hz, 1H), 7.34 (m, 5H), 6.89 (m, 2H), 5.56 (t, J=7.8Hz, 1H), 4.88 (s), 4.09 (m, 2H), 3.69 (m, 5H), 3.32 (m, 4H), 3.16 (t, J=11.8Hz, 2H), 2.94 (m, 2H), 2.51 (d, J=10.2Hz, 2H), 2.12 (m, 2H). Mp: 237-244°C ($C_{25}H_{31}FN_4O_3.3HCl.H_2O$).

Example 43

3-[N-[2-Chloro-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-3-phenylpropionic acid

Following a similar procedure to that described in example 39, but using ethyl 3-amino-3-phenylpropionate instead of β-alanine *tert*-butyl ester, and carrying out the final hydrolysis with 5N HCl at room temperature overnight, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.40 (m, 6H), 7.09 (d, J=2.1Hz, 1H), 7.02 (dd, J=9.3Hz, J=2.3Hz, 1H), 5.55 (t, J=7.8Hz, 1H), 4.87 (s), 4.00 (m, 2H), 3.67 (m, 5H), 3.31 (m, 4H), 3.15 (t, J=11.8Hz, 2H), 2.90 (m, 2H), 2.50 (d, J=10.2Hz, 2H), 2.14 (m, 2H). Mp: 167-175°C ($C_{25}H_{31}ClN_4O_3.3HCl.H_2O$).

Example 44

3-[N-[2-Methyl-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-3-phenylpropionic acid

Following a similar procedure to that described in example 37 (steps a-d), but using ethyl 3-amino-3-phenylpropionate instead of β-alanine *tert*-butyl ester, and carrying out the final hydrolysis with 5N HCl at room temperature overnight, the title compound was obtained, which was purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3 10:5:1).

^{1}H NMR (300MHz, CD_3OD+D_2O) δ (TMS): 7.35 (m, 6H), 6.87 (m, 2H), 5.39 (t, J=7.8Hz, 1H), 4.67 (m), 3.50 (d, J=10.2Hz, 2H), 3.31 (m, 5H), 3.02 (t, J=11.8Hz, 2H), 2.70 (m, 6H), 2.34 (s, 3H), 2.20 (d, J=10.2Hz, 2H), 1.75 (m, 2H). Mp: 187-233°C ($C_{27}H_{34}N_4O_3.2HCl$).

Example 45

3-[N-[4-[4-(4-Piperidinyl)piperazin-1-yl]benzoyl]amino]-2(*S*)-[(2-thienylcarbonyl)amino]propionic acid

a) Methyl 2(*S*)-amino-3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl)piperazin-1-yl]benzoyl]amino]propionate

To a mixture of the compound obtained in example 31c (1.5 g, 3.85 mmol) and N-hydroxysuccinimide (0.45 g, 3.9 mmol) in CH_2Cl_2 (50 mL), cooled in an ice bath, was added dicyclohexylcarbodiimide (0.8 g) and the mixture was then stirred at room temperature overnight. The insoluble material was filtered off and the filtrate was evaporated to dryness, yielding 1.71 g of a crude product.

To a solution of methyl 2(*S*)-2,3-diaminopropionate dihydrochloride (0.45 g, 2.22 mmol) in CH_2Cl_2 (25 mL), cooled in an ice bath, was added NEt_3 (0.8 mL) and the mixture was stirred at room temperature for 1 h. The resulting solution was placed again in an ice bath and the crude product obtained above (0.9 g, 1.85 mmol) in CH_2Cl_2 (5 mL) was added thereto. The reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with CH_2Cl_2, 0.5N NaOH was added and it was extracted with CH_2Cl_2 (2x). The combined organic extracts were dried and concentrated to afford 1.2 g of a crude product. This was purified by chromatography on silica gel ($CHCl_3$-MeOH, 5%), yielding 0.18 g of the desired product.

^1H NMR (300MHz, CD_3OD δ (TMS): 7.88 (d, J=8.8Hz, 2H), 6.97 (d, J=8.8Hz, 1H), 4.9 (COOH), 4.16 (m, 2H), 3.39 (m, 4H), 2.85 (m, 6H), 2.61 (m, 1H), 1.98 (d, J=10.5Hz, 2H), 1.47 (s, 9H), 1.41 (m, 2H).

b) Methyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl)piperazin-1-yl]benzoyl]amino]-2(*S*)-[(2-thienylcarbonyl)amino]propionate

To a solution of the compound obtained in step a) (0.18 g, 0.37 mmol) in $CHCl_3$ (15 mL) and NEt_3 (0.1 mL), cooled in an ice bath, was added dropwise 2-thienylcarbonyl chloride (0.06 mL, 0.55 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting mixture was partitioned between 0.5N NaOH and $CHCl_3$ and was extracted with $CHCl_3$ (2x). The combined organic extracts were dried and concentrated to afford a crude product (0.25 g) that was purified by chromatography on silica gel ($CHCl_3$-MeOH, 2%), yielding 70 mg of the desired compound.

c) Title compound

The compound obtained in step b) was hydrolyzed by treatment with 5N HCl at room temperature overnight to give the title compound.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.77 (m, 3H), 7.67 (dd, J=1.0Hz, J=5.0Hz, 1H), 7.15 (t, J=3.7Hz, 1H), 7.05 (d, J=8.9Hz, 2H), 4.84 (broad s), 4.82 (m, 1H), 4.08 (m, 2H), 3.92 (m, 2H), 3.67 (m, 9H), 3.15 (t, J=11.8Hz, 2H), 2.50 (d, J=10.2Hz, 2H), 2.12 (m, 2H).

Example 46

3-[N-[2-Benzylamino-4-(4,4'-bipiperidin-1-yl)benzoyl]amino]propionic acid

a) Ethyl 3-[N-[2-benzylamino-4-[1'-(*tert*-butoxycarbonyl)-4,4'-bipiperidin-1-yl]benzoyl]amino]propionate

To a solution of the compound obtained in reference example 2 (0.7 g, 1.32 mmol) in $CHCl_3$ (20 mL) and NEt_3 (0.18 mL), cooled in an ice bath, was added benzyl bromide (0.16 mL, 1.3 mmol) and the reaction mixture was refluxed overnight. The resulting mixture was partitioned between 0.5N NaOH and $CHCl_3$ and was extracted with $CHCl_3$ (2x). The combined organic extracts were dried and concentrated, yielding 1.02 g of a crude product. This was purified by chromatography on silica gel (EtOAc) to afford 0.29 g of the desired compound (38%).

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 5N HCl in EtOH at room temperature overnight and then at 40 ºC for 2 h to give the title compound.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.69 (s, 1H), 7.34 (m, 7H), 4.89 (broad s), 4.51 (s, 2H), 3.68(m, 2H), 3.60 (m, 2H), 3.32 (m, 4H), 3.02 (m, 2H), 2.65 (t, J=6.7Hz, 2H), 2.04 (m, 2H), 1.65 (m, 8H). Mp: 28-38ºC ($C_{27}H_{36}N_4O_3.2HCl.6H_2O$).

Example 47

1-[4-[4-(4-Piperidinyl)piperazin-1-yl]benzoyl]piperidin-3-carboxylic acid

a) Ethyl 1-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]piperidin-3-carboxylate

To a solution of the compound obtained in example 31c (0.7 g, 1.79 mmol) in anhydrous DMF (10 mL), cooled in an ice bath, was added ethyl nipecotate (0.33 g, 1.79 mmol) and 1-hydroxybenzotriazole (0.21 g). Finally, dicyclohexylcarbodiimide (0.36 g) was added and the reaction mixture was stirred at room temperature overnight. The insoluble material was filtered off and DMF was removed. The resulting crude product was partitioned between 1N NaOH and $CHCl_3$ and was extracted with $CHCl_3$ (3x). The combined organic extracts were dried and concentrated to a crude product that was purified by chromatography on silica gel ($CHCl_3$-MeOH, 5%). 1.1 g of the desired compound was obtained.

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 5N HCl at 60 °C for 6 h and then at room temperature overnight to give the title compound, which was purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3 10:5:1).

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.41 (d, J=8.7Hz, 2H), 7.11 (d, J=8.7Hz, 2H), 4.88 (s), 4.04 (m, 2H), 3.66 (m, 5H), 3.31 (m, 8H), 2.52 (m, 3H), 2.14 (m, 4H), 1.83 (m, 4H). Mp: 255-264°C ($C_{22}H_{32}N_4O_3.H_2O$).

Example 48

2(S)-(Benzyloxycarbonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) *Tert*-butyl 3-amino-2(S)-(benzyloxycarbonylamino)propionate

To a suspension of 3-amino-2(S)-(benzyloxycarbonylamino)propionic acid (4 g, 0.016 mol) in *tert*-butyl acetate (24 mL), cooled to 0 °C, was added 60% perchloric acid (24 mL) and the mixture was stirred at room temperature for 18 h. The resulting solution was partitioned between $NaHCO_3$ and EtOAc. The organic layer was separated, dried and concentrated to give 3.4 g of an oil. This was dissolved in THF (6 mL) and 1N NaOH (6 mL) and was heated for 1 h at 60 °C. The resulting solution was extracted with $CHCl_3$, and the organic layer was separated, dried and concentrated to give 1.9 g of the desired compound.

^1H NMR (300MHz, $CDCl_3$) δ (TMS): 7.32 (m, 5H), 5.77 (m, 1H), 5.11 (s, 2H), 4.24 (m, 1H), 3.03 (m, 2H), 1.46 (s, 9H), 1.24 (s, 2H).

b) *Tert*-butyl 2(S)-(benzyloxycarbonylamino)-3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]propionate

Following a similar procedure to that described in reference example 2a, but using the compound obtained in example 31c instead of 4-fluoro-2-nitrobenzoic acid and the compound obtained in step a) instead of β-alanine ethyl ester, the desired compound was obtained.

c) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step b), the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.75 (d, J=8.9Hz, 2H), 7.27 (m, 5H), 7.05 (d, J=8.9Hz, 2H), 5.10 (d, J=12.5, 1H), 5.03 (d, J=12.5, 1H), 4.85 (broad s, 10H), 4.48 (m, 1H), 3.82 (dd, J=10Hz, J=4.7Hz, 1H), 3.60 (m, 12H), 3.12 (t, J=12.1Hz, 2H), 2.45 (d, J=10.2Hz, 2H), 2.02 (m, 2H). Mp: 189-194°C ($C_{27}H_{35}N_5O_5.2CF_3COOH.\ 2H_2O$).

Example 49

2(S)-(Isovalerylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) ***Tert*-butyl 2(S)-amino-3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]propionate**

To a solution of the compound obtained in example 48b (2.8 g, 4.2 mmol) in EtOH (60 mL) was added acetic acid (0.05 mL) and 10% Pd/C catalyst (160 mg) and the mixture was hydrogenated at room temperature for 48 h. The catalyst was filtered off, the solvent was removed and the resulting crude product (2.29 g) was purified by chromatography on silica gel ($CHCl_3$:MeOH, 8%), to give 1.8 g (80%) of the desired compound as a white solid.

^{1}H NMR (300MHz, $CDCl_3$) δ (TMS): 7.69 (d, J=8.9Hz, 2H), 6.87 (d, J=8.9Hz, 2H), 6.71 (t, J=5.2Hz, 1H), 4.16 (m, 2H), 3.79 (m, 1H), 3.59 (m, 1H), 3.49 (m, 1H), 3.29 (m, 4H), 2.71 (m, 6H), 2.29 (m, 5H), 1.86 (d, J=10.2Hz, 2H), 1.49 (s, 18H), 1.47 (m, 2H).

b) ***Tert*-butyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]-2(S)-(isovalerylamino)propionate**

Following a similar procedure to that described in example 45b, but starting from the compound obtained in step a) and using isovaleric acid chloride instead of 2-thienylcarbonyl chloride, the title compound was obtained.

c) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step b), the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.76 (d, J=8.9Hz, 2H), 7.04 (d, J=8.9Hz, 2H), 4.84 (broad s, 10H), 4.67 (m, 1H), 3.76 (m, 2H), 3.50 (m, 11H), 3.11 (t, J=12.1Hz, 2H), 2.45 (d, J=10.2Hz, 2H), 2.09 (m, 5H), 0.92 (m, 6H). Mp: 149-151°C

($C_{24}H_{37}N_5O_4.2CF_3COOH.\ 2H_2O$).

Example 50

3-[N-[4-[4-(4-Piperidinyl)piperazin-1-yl]benzoyl]amino]-2(S)-[(2-thienyl)sulfonylamino]propionic acid

a) ***Tert*-butyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]- 2(S)-[(2-thienyl)sulfonylamino]propionate**

Following a similar procedure to that described in example 45b, but starting from the compound obtained in example 49a and using 2-thienylsulfonyl chloride instead of 2-thienylcarbonyl chloride, the title compound was obtained.

b) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step a), the title compound was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.73 (d, J=8.9Hz, 2H), 7.64 (dd, J=5.0Hz, J= 1.3Hz, 1H), 7.57 (dd J=3.7Hz, J=1.2Hz, 1H), 7.01 (m, 3H), 4.85 (broad s, 10H), 4.22 (m, 1H), 3.72 (dd, J=10Hz, J=4.7Hz, 1H), 3.50 (m, 12H), 3.12 (t, J=12.1Hz, 2H), 2.44 (d, J=10.2Hz, 2H), 2.02 (m, 2H). Mp: 156-160°C ($C_{23}H_{31}N_5O_5S_2.2CF_3COOH.\ 2H_2O$).

Example 51

2(S)-(Phenylsulfonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) **Methyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]- 2(S)-(phenylsulfonylamino)propionate**

Following a similar procedure to that described in reference example 2a, but using the compound obtained in example 31c instead of 4-fluoro-2-nitrobenzoic acid and the compound obtained in reference example 5 instead of β-alanine ethyl ester, the title compound was obtained.

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 5N HCl at room temperature for 48 h and then at 60 °C for 2 h to give the title compound.

^1H NMR (300MHz, CD_3OD+D_2O) δ (TMS): 7.79 (d, J=8.9Hz, 2H), 7.68 (d, J=8.9Hz,

2H), 7.47 (m, 3H), 7.07 (d, J=8.9Hz, 2H), 4.78 (broad s, 9H), 4.18 (m, 1H), 3.74 (dd, J=13.7Hz, J=4.8Hz, 1H), 3.64 (m, 11H), 3.47 (dd, J=13.7Hz, J=9.0Hz, 1H), 3.18 (t, J=12.1Hz, 2H), 2.50 (d, J=10.2Hz, 2H), 2.07 (m, 2H). Mp: 214-219°C ($C_{25}H_{33}N_5O_5S$ .3HCl .H_2O).

Example 52

2(S)-[(4-Methoxybenzoyl)amino]-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) ***Tert*-butyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]- 2(S)-[(4-methoxybenzoyl)amino]propionate**

Following a similar procedure to that described in example 45b, but starting from the compound obtained in example 49a and using 4-methoxybenzoyl chloride instead of 2-thienylcarbonyl chloride, the title compound was obtained.

b) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step a), the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.82 (d, J=8.9Hz, 2H), 7.77 (d, J=8.9Hz, 2H), 7.02 (d, J=8.9Hz, 2H), 6.96 (d, J=8.9Hz, 2H), 4.84 (broad s, 10H), 4.79 (m, 1H), 3.88 (m, 2H), 3.84 (s, 3H), 3.47 (m, 11H), 3.10 (t, J=12.1Hz, 2H), 2.44 (d, J=10.2Hz, 2H), 2.00 (m, 2H). Mp: 156-160°C ($C_{27}H_{35}N_5O_5.2CF_3COOH.\ 2H_2O$).

Example 53

2-Methyl-3-[N-[6-[4-(4-piperidinyl)piperazin-1-yl]nicotinoyl]amino]propionic acid

Following a similar procedure to that described in example 34, but using methyl 3-amino-2-methylpropionate instead of β-alanine *tert*-butyl ester, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD+D_2O) δ (TMS): 8.51 (d, J=2.3Hz, 1H), 7.95 (dd, J=8.9Hz, J=2.4Hz, 1H), 6.87 (d, J=9.19Hz, 1H), 4.76 (m, 7H), 3.72 (m, 4H), 3.50 (m, 5H), 3.04 (t, J=12.1Hz, 2H), 3.00 (m, 4H), 2.69 (q, J=7.2Hz, 1H), 2.26 (d, J=13.1Hz, 2H), 1.80 (m, 2H), 1.15 (d, J=7.0Hz, 3H). Mp: 138-143°C ($C_{19}H_{29}N_5O_3$ .2HCl .H_2O).

Example 54

3-[N-[4-[4-(Piperazin-1-yl)piperidin-1-yl]benzoyl]amino]butyric acid

a) 1-(*Tert*-butoxycarbonyl)-4-[1-(benzyloxycarbonyl)piperidin-4-yl]piperazine

Following a similar procedure to that described in example 30c, but starting from 1-(*tert*-butoxycarbonyl)piperazine and 1-(benzyloxycarbonyl)piperidin-4-one (prepared from 4-piperidone by treatment with benzyl chloroformate), the desired product was obtained.

b) 1-(*Tert*-butoxycarbonyl)-4-(piperidin-4-yl)piperazine

To a solution of the compound obtained in step a) (10 g, 24.6 mmol) in EtOH (100 mL) was added 10% Pd/C catalyst (0.4 g) and the mixture was hydrogenated at room temperature overnight. The catalyst was filtered off and the filtrate was concentrated to give 5.27 g of the desired compound .

c) Ethyl 4-[4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]piperidin-1-yl]benzoate

To a solution of the compound obtained in step b) (3.77 g, 14 mmol) in anhydrous DMSO (30 mL) and diisopropylethylamine (2.45 mL), was added ethyl 4-fluorobenzoate (2.35 g, 14 mmol) and the mixture was heated at 130°C overnight. DMSO was removed and the resulting residue was partitioned between 1N NaOH and $CHCl_3$ and was extracted with $CHCl_3$ (2x). The combined organic extracts were concentrated to give 6.95 g of a crude product that was directly used in the next step as obtained.

d) 4-[4-[4-(*Tert*-butoxycarbonyl)piperazin-1-yl]piperidin-1-yl]benzoic acid

The crude product obtained in step c) was treated with 1N NaOH (40 mL) in MeOH (40 mL) at reflux overnight. MeOH was removed and the residue was neutralized with 10% $NaHSO_4$ in an ice bath. The resulting solution was allowed to stand in the refrigerator overnight. The precipitate was collected by filtration and dried to give 3.64 g of the desired compound .

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.85 (d, J=8.9Hz, 2H), 6.93 (d, J=8.9Hz, 2H), 4.84 (broad s), 3.98 (d, J=10.2Hz, 2H), 3.45 (m, 4H), 2.87 (t, J=12.1Hz, 2H), 2.65 (m, 4H), 2.56 (m, 1H), 2.06 (d, J=10.2Hz, 2H), 1.66 (m, 2H), 1.45 (s, 9H).

e) Ethyl 3-[N-[4-[4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]piperidin-1-yl]benzoyl]amino]butyrate

Following a similar procedure to that described in reference example 2a, but starting from the compound obtained in step d) and using ethyl 3-

aminobutyrate instead of β-alanine ethyl ester, the desired product was obtained.

f) Title compound

The compound obtained in step e) was hydrolyzed by treatment with 5N HCl at room temperature overnight and then at 60 °C for 2 h. The resulting crude product was purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3, 10:5:1) to give the title compound.

^1H NMR (300MHz, $DMSO_{d6}$) δ (TMS): 8.17 (d, J=8.1Hz, 1H), 7.68 (d, J=8.8Hz, 2H), 6.93 (d, J=8.9Hz, 2H), 4.27 (m, 1H), 3.85 (d, J=12.9Hz, 2H), 3.20 (m, 6H), 2.80 (m, 4H), 2.70 (t, J=11.2Hz, 2H), 2.49 (m, 5H), 2.34 (dd, J=15.0Hz, J=7.2Hz, 1H), 1.79 (d, J=11.2Hz, 2H), 1.43 (m, 2H), 1.14 (d, J=6.6Hz, 3H). Mp: 230-237°C ($C_{20}H_{30}N_4O_3$. HCl. H_2O).

Example 55

3-Methyl-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]butyric acid

Following a similar procedure to that described in example 31, but using methyl 3-amino-3-methylbutyrate (prepared from methyl 3-carboxy-3-methylbutyrate by Curtius rearrangement with diphenylfosforylazide) instead of ethyl 3-aminobutyrate, and carrying out the final hydrolysis with 5N HCl in MeOH at room temperature for 48 h, the desired product was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.71 (d, J=8.9Hz, 2H), 6.95 (d, J=8.9Hz, 2H), 4.98 (m, 11H), 3.45 (d, J=12.1Hz, 2H), 3.33 (m, 4H), 3.04 (t, J=12.1Hz, 2H), 2.76 (m, 4H), 2.66 (m, 1H), 2.57 (s, 2H), 2.08 (d, J=13.1Hz, 2H), 1.81 (m, 2H), 1.54 (s, 6H).

Example 56

3-[N-[4-[4-(Piperazinyl)piperidin-1-yl]benzoyl]amino]-2(S)-[(2-thienylcarbonyl)amino]propionic acid

Following a similar procedure to that described in example 54, but using the compound obtained in reference example 8 instead of ethyl 3-aminobutyrate, the desired product was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.93 (d, J=8.8Hz, 2H), 7.76 (d, J=3Hz, 1H), 7.66 (m, 3H), 7.13 (t, J=4.3Hz, 1H), 4.90 (broad s, 11H), 4.83 (m, 1H), 3.85 (m, 13H), 3.61 (t, J=10.6Hz, 2H), 2.56 (d, J=12.2Hz, 2H), 2.39 (m, 2H). Mp: 180-187°C

($C_{24}H_{31}N_5O_4S.3\ HCl.\ 2H_2O$).

Example 57

3-[N-[4-[4-(4-Piperidinyl)piperazin-1-yl]-2-trifluoromethylbenzoyl]amino]-2(S)-[(2-thienylcarbonyl)amino]propionic acid

Following a similar procedure to that described in example 31, but starting from ethyl 4-fluoro-2-trifluoromethylbenzoate and using the compound obtained in reference example 8 instead of ethyl 3-aminobutyrate, and carrying out the final hydrolysis with 6N HCl at room temperature overnight and then at 50 °C for 1 h, the desired product was obtained, which was purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3, 10:5:1).

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.74 (d, J=4.7Hz, 1H), 7.61 (d, J= 6.0Hz, 1H), 7.43 (d, J=8.5Hz, 1H), 7.10 (m, 3H), 4.89 (broad s, 6H), 4.62 (m, 1H), 3.80 (m, 2H), 3.41 (d, J=12.6Hz, 2H), 3.22 (m, 4H), 2.93 (t, J=12.1Hz, 2H), 2.63 (m, 4H), 2.51 (m, 1H), 1.98 (d, J=10.2Hz, 2H), 1.68 (m, 2H). Mp: 196-203°C ($C_{25}H_{30}F_3N_5O_4S.H_2O$).

Example 58

2(S)-[(2-Furoyl)amino]-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 45, but using 2-furoyl chloride instead of 2-thienylcarbonyl chloride, the title compound was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.75 (d, J=8.9Hz, 2H), 7.68 (s, 1H), 7.12 (dd, J=2.8Hz, J= 0.7Hz, 1H), 7.04 (d, J=8.9Hz, 2H), 6.58 (dd J=3.4Hz, J=1.7Hz, 1H), 4.88 (broad s, 11H), 4.80 (m, 1H), 4.05 (m, 2H), 3.97 (dd, J=10Hz, J=4.0Hz, 1H), 3.83 (dd, J=10Hz, J=6.5Hz, 1H), 3.73 (m, 2H), 3.65 (d, J=10.2Hz, 2H), 3.31 (m, 5H), 3.16 (t, J=12.1Hz, 2H), 2.49 (d, J=10.2Hz, 2H), 2.12 (m, 2H). Mp: 196-200°C ($C_{24}H_{31}N_5O_5.3HCl.2H_2O$).

Example 59

2(S)-[(3-Furoyl)amino]-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 45, but using 3-furoyl chloride instead of 2-thienylcarbonyl chloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 8.08 (s, 1H), 7.76 (d, J=8.9Hz, 2H), 7.56 (t, J= 1.5Hz, 1H), 7.04 (d, J=8.9Hz, 2H), 6.80 (dd J=1.9Hz, J=0.8Hz, 1H), 4.88 (broad s, 9H), 4.79 (m, 1H), 4.05 (m, 2H), 3.89 (dd, J=10Hz, J=4.0Hz, 1H), 3.84 (dd, J=10Hz, J=6.5Hz, 1H), 3.73 (m, 2H), 3.63 (d, J=10.2Hz, 2H), 3.31 (m, 5H), 3.14 (t, J=12.1Hz, 2H), 2.48 (d, J=10.2Hz, 2H), 2.12 (m, 2H). Mp: 201-205°C ($C_{24}H_{31}N_5O_5.3HCl.H_2O$).

Example 60

2(S)-(n-Butoxycarbonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-2-trifluoromethylbenzoyl]amino]propionic acid

Following a similar procedure to that described in example 31, but starting from ethyl 4-fluoro-2-trifluoromethylbenzoate and using the compound obtained in reference example 9 instead of ethyl 3-aminobutyrate, and then carrying out the final hydrolysis with 6N HCl at room temperature overnight and then at 60 °C for 2 h, the desired product was obtained, which was purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3, 10:5:1).

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.45 (d, J=8.5Hz, 1H), 7.19 (s, 1H), 7.13 (d, J=8.6Hz, 1H), 4.80 (broad s, 10H), 4.26 (m, 1H), 4.04 (t, J=5.4Hz, 2H), 3.75 (dd, J=10Hz, J=4.0Hz, 1H), 3.66 (dd, J=10Hz, J=6.5Hz, 1H), 3.38 (d, J=12.9Hz, 2H), 3.30 (m, 4H), 3.03 (t, J=10.2Hz, 2H), 2.79 (m, 4H), 2.68 (t, J=8.5Hz, 1H), 2.12 (d, J=15.7Hz, 2H), 1.79 (m, 2H), 1.60 (m, 2H), 1.39 (m, 2H), 0.92 (t, J=7.3Hz, 3H). Mp: 154-160°C ($C_{25}H_{36}F_3N_5O_5.3\,H_2O$).

Example 61

2(S)-(n-Butoxycarbonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 31, but using the compound obtained in reference example 9 instead of ethyl 3-aminobutyrate, and carrying out the final hydrolysis with 6N HCl at room temperature overnight and then at 60°C for 2 h, the desired product was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.72 (d, J=8.8Hz, 2H), 6.95 (d, J=8.6Hz, 2H), 4.79 (broad s, 11H), 4.27 (m, 1H), 4.01 (m, 2H), 3.72 (m, 2H), 3.45 (d, J=12.9Hz, 2H),

3.31 (m, 4H), 2.99 (t, J=11.4Hz, 2H), 2.76 (m, 4H), 2.65 (t, J=8.5Hz, 1H), 2.10 (d, J=12.7Hz, 2H), 1.77 (m, 2H), 1.56 (m, 2H), 1.35 (m, 2H), 0.89 (t, J=7.3Hz, 3H). Mp: 167-173°C ($C_{24}H_{37}N_5O_5 . 3.5H_2O$).

Example 62

2(S)-(n-Butoxycarbonylamino)-3-[N-[4-[4-(piperazin-1-yl)piperidin-1-yl]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 54, but using the compound obtained in reference example 9 instead of ethyl 3-aminobutyrate, the desired product was obtained.

^1H NMR (300MHz, CD_3OD) δ (TMS): 7.83 (d, J=8.8Hz, 2H), 7.32 (d, J=8.8Hz, 2H), 4.86 (broad s, 12H), 4.44 (m, 1H), 4.02 (m, 4H), 3.71 (m, 11H), 3.30 (m, 2H), 2.42 (d, J=12.2Hz, 2H), 2.13 (m, 2H), 1.57 (m, 2H), 1.39 (m, 2H), 0.92 (m, 3H). Mp: 185-197°C ($C_{24}H_{37}N_5O_5.2HCl.3H_2O$).

Example 63

N-[2-[4-[4-(4-Piperidinyl)piperazin-1-yl]phenyl]acetyl]-L-leucine

a) Ethyl 2-(4-aminophenyl)acetate

To a solution of 2-(4-aminophenyl)acetic acid (20 g, 13.23 mmol) in EtOH (300 mL), cooled in an ice bath, was added concentrated H_2SO_4 (26.67 mL) and the mixture was refluxed for 12 h. EtOH was removed, and the residue was made basic with 5N NaOH in an ice bath and was extracted with $CHCl_3$ (3x). The combined organic extracts were dried and concentrated to give 19.9 g of a crude product that was directly used in the next step as obtained.

b) Ethyl 2-[4-(piperazin-1-yl)phenyl]acetate

A mixture of the compound obtained in step a) (18.15 g, 10.13 mmol) and bis(2-chloroethyl)amine (17.77 g, 10.12 mmol) in n-BuOH (100 mL) was refluxed overnight. Next, K_2CO_3 (7 g) was added and the mixture was again refluxed overnight. The remaining K_2CO_3 was filtered off, the filtrate was concentrated and the resulting residue was partitioned between 1N NaOH and $CHCl_3$ and was extracted with $CHCl_3$ (2x). The combined organic extracts were dried and concentrated to give 36.1 g of a crude product. This was purified by chromatography on silica gel ($CHCl_3$: MeOH:NH_3, 60:5:0.2), yielding 16.8 g of the desired compound .

c) Ethyl 2-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]acetate

Following a similar procedure to that described in example 30c, but starting from the compound obtained in step b), the desired compound was obtained.

d) 2-[4-[4-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]acetic acid

The compound obtained in step c) was hydrolyzed by treatment with 5N NaOH in EtOH at reflux for 12 h to give the desired product.

^{1}H NMR (300MHz, $CDCl_3$+CD_3OD) δ (TMS): 7.71 (s, 1H), 7.17 (d, J=8.4Hz, 2H), 6.84 (d, J=8.9Hz, 2H), 4.77 (broad s), 4.16 (d, J=13.1Hz, 2H), 3.44 (s, 2H), 3.14 (m, 4H), 2.91 (m, 4H), 2.72 (m, 3H), 1.98 (d, J=13.1Hz, 2H), 1.55 (m, 2H), 1.50 (s, 9H).

e) N-[2-[4-[4-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]acetyl]-L-leucine ethyl ester

To a solution of the compound obtained in step d) (0.7 g, 1.7 mmol) in DMF (20 mL) was added 1-hydroxybenzotriazole (0.25 g) and dicyclohexylcarbodiimide (0.34 g) and the mixture was stirred at room temperature for 1 h. The mixture was then placed in an ice bath and NEt_3 (0.35 mL) and L-leucine ethyl ester hydrochloride (0.33 g, 1.7 mmol) were added. The reaction mixture was stirred at room temperature for 48 h. The insoluble material was filtered off and DMF was removed. The resulting crude product was partitioned between aqueous 0.2M $NaHCO_3$ solution and $CHCl_3$ and was extracted with $CHCl_3$ (2x). The combined organic extracts were dried and concentrated to give 0.9 g of a crude product. This was purified by chromatography on silica gel ($CHCl_3$-MeOH, 4%), yielding 0.58 g of the desired compound.

f) Title compound

The compound obtained in step e) was hydrolyzed by treatment with 6N HCl at room temperature overnight and then at 50 °C for 1 h. The solution was brought to pH 6-7 with 5N NaOH and the resulting solution was evaporated to dryness. The residue was taken up in a mixture $CHCl_3$-MeOH 10:4, filtered and purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3, 10:4:1) to give the title compound.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.20 (d, J=8.9Hz, 2H), 6.91 (d, J=8.9Hz, 2H), 4.86 (m, 4H), 4.27 (m, 1H), 3.47 (d, J=15.1Hz, 1H), 3.44 (d, J=15.1Hz, 1H), 3.29 (m, 2H), 3.17 (m, 4H), 2.85 (t, J=12.1Hz, 2H), 2.72 (m, 4H), 2.45 (m, 1H), 2.02 (d, J=13.1Hz, 2H), 1.60 (m, 5H), 0.90 (t, J=5.3Hz, 6H). Mp: 237-238°C ($C_{23}H_{36}N_4O_3.0.25H_2O$).

Example 64

N-[2-[4-[4-(4-Piperidinyl)piperazin-1-yl]phenyl]acetyl]-L-tyrosine

Following a similar procedure to that described in example 63, but using L-tyrosine methyl ester hydrochloride instead of L-leucine ethyl ester hydrochloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD+D_2O) δ (TMS): 7.02 (d, J=8.4Hz, 2H), 6.91 (d, J=8.4Hz, 2H), 6.88 (d, J=8.4Hz, 2H), 6.63 (d, J=8.4Hz, 2H), 4.78 (m, 6H), 4.41 (m, 1H), 3.50 (d, J=15.1Hz, 2H), 3.41 (m, 2H), 3.29 (m, 5H), 3.14 (m, 2H), 2.95 (m, 4H), 2.83 (m, 2H), 2.24 (d, J=13.1Hz, 2H), 1.81 (m, 2H). Mp: 264-265°C ($C_{26}H_{34}N_4O_4.NaCl.H_2O$).

Example 65

N-[2-[4-[4-(4-Piperidinyl)piperazin-1-yl]phenyl]acetyl]-L-phenylalanine

Following a similar procedure to that described in example 63, but using L-phenylalanine ethyl ester hydrochloride instead of L-leucine ethyl ester hydrochloride, the title compound was obtained.

Mp: 235-242°C ($C_{26}H_{34}N_4O_3.2.5\ H_2O$).

Example 66

N-Methyl-N-[2-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]acetyl]glycine

Following a similar procedure to that described in example 63, but using N-methylglycine methyl ester hydrochloride instead of L-leucine ethyl ester hydrochloride, the title compound was obtained.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 7.25 (m, 4H), 4.93 (m, 15H), 4.12 (s, 2H), 3.80 (s, 2H), 3.70 (m, 9H), 3.62 (d, J=15.1Hz, 2H), 3.18 (m, 2H), 3.16 (s 3H), 2.50 (d, J=13.1Hz, 2H), 2.15 (m, 2H). Mp: 141-146°C ($C_{20}H_{30}N_4O_3.3HCl.5H_2O$).

Example 67

N-[2-[4-[4-(4-Piperidinyl)piperazin-1-yl]phenyl]acetyl]-D-phenylalanine

Following a similar procedure to that described in example 63, but using D-phenylalanine ethyl ester hydrochloride instead of L-leucine ethyl ester hydrochloride, the title compound was obtained.

^{1}H NMR (300MHz, $CD_3OD+CDCl_3$) δ (TMS): 7.22 (m, 4H), 7.11 (m, 3H), 6.94 (m, 2H), 4.68 (m, 7H), 4.45 (m, 1H), 3.49 (d, J=15.1Hz, 2H), 3.41 (m, 2H), 3.19 (m, 4H), 3.05 (m, 4H), 2.85 (m, 4H), 2.67 (m, 1H), 2.24 (d, J=13.1Hz, 2H), 1.81 (m, 2H). Mp: 253-257°C ($C_{26}H_{34}N_4O_3$. $2H_2O$).

Example 68

2(S)-(Benzylsulfonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) Methyl 2(S)-(benzylsulfonylamino)-3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]propionate

Following a similar procedure to that described in reference example 2a, but using the compound obtained in example 31c instead of 4-fluoro-2-nitrobenzoic acid and the compound obtained in reference example 12 instead of β-alanine ethyl ester, the desired compound was obtained.

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 6N HCl at room temperature overnight and then at 40 °C for 1 h to give the title compound.

^{1}H NMR (300MHz, $DMSO_{d6}$) δ (TMS): 8.28 (m, 1H), 7.91 (d, J=8.9Hz, 2H), 7.65 (m, 12H), 7.35 (m, 5H), 6.91 (d, J=8.9Hz, 2H), 4.37 (d, J=13.7Hz, 1H), 4.31 (d, J=13.7Hz, 1H), 3.84 (m, 1H), 3.20 (m, 9H), 2.80 (t, J=12.1Hz, 2H), 2.55 (m, 4H), 1.85 (d, J=10.2Hz, 2H), 1.68 (m, 2H). Mp: 247-249°C ($C_{25}H_{35}N_5O_5S.ClNH_4.2H_2O$).

Example 69

2(S)-(Benzyloxycarbonylamino)-3-[[N-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]amino]carbonyl]propionic acid

a) 1-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]-4-(4-nitrophenyl)piperazine

Following a similar procedure to that described in example 31c, but starting from 1-(4-nitrophenyl)piperazine instead of the compound obtained in example 31b, the desired compound was obtained.

b) 1-(4-Aminophenyl)-4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazine

To a mixture of the compound obtained in step a) (10.3 g, 26.3 mmol) and EtOH (500 mL) was added anhydrous $SnCl_2$ (24.82 g) and $NaBH_4$ (0.5 g) and the reaction mixture was heated at 60 °C for 8 h. EtOH was removed and the residue was partitioned between 2N NaOH and $CHCl_3$ and was extracted with $CHCl_3$ (3x). The resulting residue was suspended in EtOH, and upon cooling, a solid precipitated. This solid was collected by filtration, washing with EtOH, to afford 3 g of the desired product. The ethanolic washes were concentrated and the resulting residue (4.5 g) was purified by chromatography on silica gel ($CHCl_3$-MeOH, 5%), to afford further 4 g of the desired compound .

^1H NMR (300MHz, $CDCl_3$) δ (TMS): 6.81 (d, J=8.9Hz, 2H), 6.65 (d, J=8.9Hz, 2H), 4.14 (m, 2H), 3.40 (m, 1H), 3.06 (m, 4H), 2.76 (m, 6H), 2.42 (m, 1H), 1.86 (d, J=13.1Hz, 2H), 1.45 (s, 9H), 1.42 (m, 2H).

c) 3-(Benzyloxycarbonyl)-4(S)-[[[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]aminocarbonyl]methyl]oxazolidin-5-one

To a solution of N-benzyloxycarbonyl-L-aspartic acid (10 g, 37.4 mmol) in toluene (200 mL) was added paraformaldehyde (2.25 g, 30.3 mmol) and *p*-toluenesulfonic acid (0.44 g) and the reaction mixture was refluxed in a Dean-Stark overnight. To the resulting solution was added EtOAc (150 mL) and this was washed with 0.06M K_2CO_3 and then with H_2O (3x). The organic phase was dried and cocentrated to afford 11.2 g of 2-(3-benzyloxycarbonyl-5-oxooxazolidin-4(S)-yl)acetic acid as a crude product.

To a solution of this crude product (3.87 g, 13.85 mmol) in DMF (80 mL) was added 1-hydroxybenzotriazole (2 g) and dicyclohexylcarbodiimide (2.7 g) and the mixture was stirred for 1 h at room temperature. Next, the compound obtained in step b) (5 g, 13.86 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. The insoluble material was filtered off, DMF was removed and the resulting residue was partitioned between 0.2M $NaHCO_3$ and $CHCl_3$ and was extracted with $CHCl_3$ (2x). The combined organic extracts were dried and concentrated to give 10.86 g of a crude product. This was purified by chromatography on silica gel ($CHCl_3$-MeOH, 5%) to afford 5.62 g of the desired compound.

d) Title compound

The compound obtained in step c) was hydrolyzed by treatment with 6N HCl at room temperature overnight and then at 40 °C for 1 h to give the title compound.

^{1}H NMR (300MHz, CD_3OD+D_2O+TFA) δ (TMS): 7.43 (d, J=8.9Hz, 2H), 7.28 (m, 5H), 7.05 (d, J=8.9Hz, 2H), 5.33 (m, 5H), 5.07 (m, 2H), 4.62 (m, 1H), 3.65 (m, 11H), 3.12 (t, J=13.2 Hz, 2H), 2.95 (m, 2H), 2.45 (d, J=13.1Hz, 2H), 2.06 (m, 2H). Mp: 253-259ºC ($C_{27}H_{35}N_5O_5.0.5H_2O$).

Example 70

2(S)-[3-(4-Fluorophenyl)ureido]-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid

a) Methyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]-2(S)-[3-(4-fluorophenyl)ureido]propionate

Following a similar procedure to that described in reference example 2a, but using the compound obtained in example 31c instead of 4-fluoro-2-nitrobenzoic acid and the compound obtained in reference example 11 instead of β-alanine ethyl ester, the title compound was obtained.

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 6N HCl 6N at room temperature overnight and then at 40 °C for 2 h to give the title compound.

^{1}H NMR (300MHz, $CD_3OD+CDCl_3$) δ (TMS): 7.77 (d, J=8.8Hz, 2H), 7.31 (m, 2H), 7.21 (m, 2H), 7.09 (d, J=8.6Hz, 2H), 4.77 (broad s, 11H), 4.52 (t, J=4.5Hz, 1H), 3.86 (q de d, J=15.6Hz, J=4.6Hz, 2H), 3.68 (m, 7H), 3.59 (m, 4H), 3.14 (t, J=12.6Hz, 2H), 2.49 (d, J=12.7Hz, 2H), 2.06 (m, 2H). Mp: 247-255ºC ($C_{26}H_{33}FN_6O_4.2HCl.\ 2H_2O$).

Example 71

2(S)-(Benzylsulfonylamino)-3-[N-[4-[4-(piperazinyl)piperidin-1-yl]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 54, but using the compound obtained in reference example 12 instead of ethyl 3-aminobutyrate, the desired product was obtained.

^{1}H NMR (300MHz, CD_3OD+$CDCl_3$) δ (TMS): 7.66 (d, J=8.8Hz, 2H), 7.38 (m, 2H), 7.31 (m, 3H), 6.85 (d, J=8.6Hz, 2H), 4.40 (broad s, 9H), 4.29 (m, 2H), 3.98 (m, 1H), 3.82 (d, J=12.5Hz, 2H), 3.65 (m, 2H), 3.15 (m, 4H), 2.80 (m, 6H), 2.55 (m, 1H), 1.88 (t, J=10.6Hz, 2H), 1.55 (t, J=8.9Hz, 2H). Mp: 231-235°C ($C_{26}H_{35}N_5O_5S$. HCl. $2H_2O$).

Example 72

2(S)-[(4-Methoxyphenyl)sulfonylamino]-3-[N-[4-[4-(piperazinyl)piperidin-1-yl]benzoyl]amino]propionic acid

Following a similar procedure to that described in example 54, but using the compound obtained in reference example 7 instead of ethyl 3-aminobutyrate, the desired product was obtained.

^{1}H NMR (300MHz, $DMSO_{d6}$) δ (TMS): 8.37 (d, J=4.8Hz, 1H), 7.68 (d, J=8.6Hz, 2H), 7.58 (d, J=8.6Hz, 2H), 7.03 (d, J=8.6Hz, 2H), 6.92 (d, J=8.6Hz, 2H), 4.32 (t, J=2.4Hz, 1H), 3.85 (d, J= 14.3Hz, 2H), 3.71 (s, 3H), 3.30 (m, 8H), 2.95 (m, 4H), 2.77 (m, 2H), 2.58 (m, 4H), 1.77 (d, J=9.8Hz, 2H), 1.42 (m, 2H). Mp: 240-247°C ($C_{26}H_{35}N_5O_6S$. H_2O).

Example 73

3-[N-[4-[4-(4-Piperidinyl)piperazin-1-yl]benzoyl]amino]-2(S)-[2-(2-thienyl)acetylamino]propionic acid

a) Methyl 3-[N-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]benzoyl]amino]-2(S)-[2-(2-thienyl)acetylamino]propionate

Following a similar procedure to that described in reference example 2a, but using the compound obtained in example 31c instead of 4-fluoro-2-nitrobenzoic acid and the compound obtained in reference example 10 instead of β-alanine ethyl ester, the title compound was obtained.

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 6N HCl at room temperature overnight and then at 50 °C for 1 h to give the title compound.

^{1}H NMR (300MHz, CD_3OD) δ (TMS): 9.14 (m, 1H), 8.72 (d, J=6.8Hz, 1H), 8.42 (d, J=8.9Hz, 2H), 8.12 (m, 1H), 7.72 (m, 3H), 4.85 (q, J=6.4Hz, 1H), 4.51 (s, 2H), 4.37 (m, 2H), 4.11 (broad s, 11H), 3.97 (m, 4H), 3.57 (t, J=11.2Hz, 2H), 3.33 (m, 4H), 3.22

(t, J=12.1Hz, 1H), 2.64 (d, J=10.2Hz, 2H), 2.39 (m, 2H). Mp: 228-231°C ($C_{25}H_{33}N_5O_4S$. HCl. 2.5H_2O).

Example 74

2-[2-Oxo-3-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]imidazolidin-1-yl]acetic acid

a) **1-[4-[4-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]-3-(2-chloroethyl)urea**

To a solution of the compound obtained in example 69b (0.8 g, 2.2 mmol) in acetonitrile (40 mL), cooled in an ice bath, was added 2-chloroethyl isocyanate (0.19 mL, 2.2 mmol) with the aid of a syringe and the resulting mixture was stirred at room temperature for 48 h. The precipitate was collected by filtration, dissolved in EtOH and then evaporated to dryness, to afford the desired product as a yellow solid.

b) **1-[4-[4-[1-(*Tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]imidazolidin-2-one**

To a solution of the compound obtained in step a) in DMF (30 mL) was added anhydrous K_2CO_3 (0.3 g), NaI (6 mg) and DMAP (5 mg), and the resulting mixture was heated at 60°C overnight. DMF was removed, H_2O was added and it was extracted with $CHCl_3$ (3x). The combined organic extracts were dried and concentrated to afford 1 g of a crude product. This was purified by chromatography on silica gel ($CHCl_3$-MeOH, 5%), yielding 0.48 g of the desired product.

c) ***Tert*-butyl 2-[3-[4-[4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]-2-oxoimidazolidin-1-yl]acetate**

To a solution of the compound obtained in step b) (0.48 g, 1.1 mmol) in DMF (25 mL) was added NaH (67 mg) in portions. When the addition was completed, the mixture was stirred at room temperature for 20 min. Next, *tert*-butyl bromoacetate (0.16 mL) was added and finally NaI (48 mg) and DMAP (48 mg). The reaction mixture was heated at 60 °C overnight, and the resulting solution was partitioned between aqueous 0.2M $NaHCO_3$ solution and CH_2Cl_2. The organic layer was dried and concentrated to a crude product that was

purified by chromatography on silica gel ($CHCl_3$-MeOH, 5%), yielding 90 mg of the desired product.

d) Title compound

Following the hydrolysis procedure described in example 1b, but starting from the compound obtained in step c), the title compound was obtained.

^1H NMR (300MHz, $DMSO_{d6}$+TFA) δ (TMS): 8.67 (m, 1H), 8.46 (m, 1H), 7.25 (d, J=9.8Hz, 2H), 7.01 (d, J=9.8Hz, 2H), 4.81 (t, J=8.9Hz, 2H), 4.40 (s, 2H), 3.97 (t, J=8.9Hz, 2H), 3.83 (m, 2H), 3.44 (m, 7H), 2.97 (m, 4H), 2.25 (d, J=10.2Hz, 2H), 1.79 (m, 2H). Mp: 168-169°C ($C_{20}H_{29}N_5O_3.3CF_3COOH$).

Example 75

N-Benzyl-N-[[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]acetyl]glycine

Following a similar procedure to that described in example 63, but using N-benzylglycine ethyl ester instead of L-leucine ethyl ester, the title compound was obtained.

^1H NMR (300MHz, $DMSO_{d6}$+TFA) δ (TMS): 8.71 (m, 1H), 8.54 (m, 1H), 7.28 (m, 3H), 7.18 (m, 2H), 7.10 (m, 2H), 6.92 (t, J=6.3Hz, 2H), 4.63 (s, 1H), 4.48 (s, 1H), 4.04 (s, 1H), 3.87 (s, 1H), 3.80 (m, 1H), 3.63 (s, 1H), 3.56 (s, 1H), 3.34 (m, 9H), 3.20 (m, 1H), 2.93 (t, J=12.4Hz, 2H), 2.27 (d, J= 11.9Hz, 2H), 1.83 (m, 2H). Mp: 239-245°C ($C_{26}H_{34}N_4O_3.\ 0.5H_2O$).

Example 76

2(S)-(Phenylsulfonylamino)-3-[[N-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]amino]carbonyl]propionic acid

Following a similar procedure to that described in example 69, but using N-phenylsulfonyl-L-aspartic acid (prepared from L-aspartic acid by treatment with benzenesulfonyl chloride in aqueous saturated $NaHCO_3$ solution) instead of N-benzyloxycarbonyl-L-aspartic acid, the title compound was obtained.

^1H NMR (300MHz, $DMSO_{d6}$+TFA) δ (TMS): 9.78 (d, J=14.0Hz, 1H), 8.69 (m, 1H), 8.45 (m, 1H), 8.11 (m, 1H), 7.78 (t, J=4.8Hz, 2H), 7.49 (m, 4H), 7.27 (d, J=8.8Hz, 1H), 6.81 (t, J=9.1Hz, 2H), 4.22 (m, 1H), 3.42 (m, 11H), 2.93 (m, 2H), 2.54 (m, 2H), 2.28 (d, J=10.2Hz, 2H), 1.80 (m, 2H). Mp: 274-275 °C ($C_{25}H_{33}N_5O_5S.\ 0.5H_2O$).

Example 77

2-[[[4-[4-(4-Piperidinyl)piperazin-1-yl]phenyl]amino]carbonyloxy]acetic acid

a) Methyl 2-[[[4-[4-[(1-*tert*-butoxycarbonyl)piperidin-4-yl]piperazin-1-yl]phenyl]amino]carbonyloxy]acetate

To a solution of the compound obtained in example 31c (1.5 g, 3.8 mmol) in benzene (25 mL) was added NEt_3 (0.43 mL) and finally diphenylfosforylazide (0.8 mL, 3.8 mmol) was slowly added with the aid of a syringe. After heating the mixture at 90 °C for 2 h, methyl glycolate (0.58 mL) was added and the reaction mixture was heated at 90°C overnight. The resulting solution was treated with cold 0.2M $NaHCO_3$ and was extracted with EtOAc (2x) and then with $CHCl_3$ (2x). The combined organic extracts were dried and concentrated to a crude product that was purified by chromatography on silica gel ($CHCl_3$-MeOH, 5%), yielding 1.0 g of the desired compound .

b) Title compound

The compound obtained in step a) was hydrolyzed by treatment with 6N HCl at room temperature overnight, and the resulting product was purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3, 10:5:1) to give the title compound.

^1H NMR (300MHz, $DMSO_{d6}$+TFA) δ (TMS): 9.60 (m, 1H), 8.73 (m, 1H), 8.57 (m, 1H), 7.35 (d, J=8.9Hz, 2H), 6.95 (d, J=8.9Hz, 2H), 4.53 (s, 2H), 3.39 (m, 11H), 2.89 (m, 2H), 2.25 (d, J=12.1Hz, 2H), 1.87 (m, 2H). Mp: 242-253°C ($C_{18}H_{26}N_4O_4$. $2ClNH_4$. $3H_2O$).

Example 78

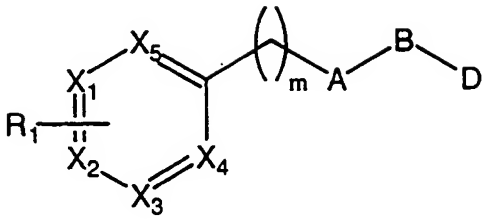
N-Benzyl-N-[[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]aminocarbonyl]glycine

Following a similar procedure to that described in example 77, but using N-benzylglycine ethyl ester instead of methyl glycolate, the title compound was obtained.

^1H NMR (300MHz, $DMSO_{d6}$) δ (TMS): 8.93 (m, 1H), 8.73 (m, 1H), 7.28 (m, 7H), 6.90 (d, J=8.9Hz, 2H), 6.47 (m, 5H), 4.57 (s, 1H), 3.97 (s, 1H), 3.41 (m, 13H), 2.92 (m, 2H), 2.28 (d, J=12.1Hz, 2H), 1.87 (m, 2H). Mp: 144-158°C ($C_{25}H_{33}N_5O_3$. $2H_2O$).

CLAIMS

1.- A compound of formula I:

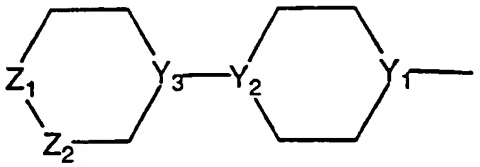


I

wherein:

one of X_1 or X_2 represents C substituted with the group R_1 and the other represents CR_2 or N, and the remaining groups X_3, X_4 and X_5 independently represent CR_2 or N, with the proviso that the ring cannot contain more than two N atoms;

R_1 represents a group of formula:



wherein the terminal ring can be optionally substituted with one or more C_{1-4} alkyl groups;

R_2 independently represent hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl, heteroarylC_{0-4} alkyl, cyano, nitro, $R_3R_4NC_{0-4}$ alkyl, $R_5SO_2NR_3C_{0-4}$ alkyl, $R_5CONR_3C_{0-4}$ alkyl, $R_5OCONR_3C_{0-4}$ alkyl, $R_3R_4NCONR_3C_{0-4}$ alkyl, $R_5SO_qC_{0-4}$ alkyl, $R_3R_4NSO_2C_{0-4}$ alkyl, $R_3R_4NCOC_{0-4}$ alkyl, R_5COC_{0-4} alkyl, $HOOCC_{0-4}$ alkyl, R_5OOCC_{0-4} alkyl, hydroxyC_{0-4} alkyl or R_5OC_{0-4} alkyl;

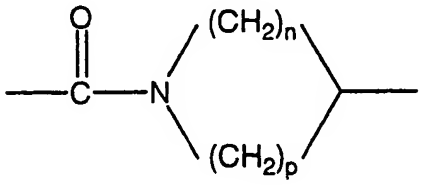
m represents 0 or 1;

A represents a group $-CONR_3-$, $-CSNR_3-$, $-SO_2NR_3-$, $-NR_3CO-$, $-NR_3CS-$, $-NR_3SO_2-$, $-NR_3COO-$, $-OCONR_3-$ or $-NR_3CONR_3-$;

B represents C_{1-4} alkylene which can be optionally substituted with one or

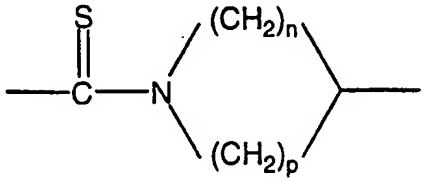
more groups independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl, arylC_{3-7} cycloalkyl, heteroarylC_{0-4} alkyl, $R_3R_4NC_{0-4}$ alkyl, $R_5SO_2NR_3C_{0-4}$ alkyl, $R_5CONR_3C_{0-4}$ alkyl, $R_5OCONR_3C_{0-4}$ alkyl, $R_3R_4NCONR_3C_{0-4}$ alkyl, $R_5SO_qC_{0-4}$ alkyl, $R_3R_4NSO_2C_{0-4}$ alkyl, $R_3R_4NCOC_{0-4}$ alkyl, R_5COC_{0-4} alkyl, $HOOCC_{0-4}$ alkyl, R_5OOCC_{0-4} alkyl, hydroxyC_{0-4} alkyl or R_5OC_{0-4} alkyl;

or A and B together can represent a group of formula (i) or (ii):



(i)

or



(ii)

R_3 and R_4 independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl or heteroarylC_{0-4} alkyl, and optionally, when A represents $-NR_3CONR_3-$, the two R_3 groups in A can be bonded together forming a C_{2-5} polymethylene chain;

R_5 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, C_{7-20} polycyclylC_{0-4} alkyl, arylC_{0-4} alkyl, arylC_{2-4} alkenyl, arylC_{3-7} cycloalkyl or heteroarylC_{0-4} alkyl;

n and p are integers 0, 1, 2 or 3 such that the sum of n plus p equals 3 to 5;

q represents 0, 1 or 2;

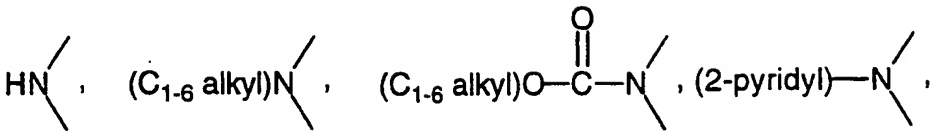
Y_1 represents N or CR_6, wherein R_6 represents hydrogen, hydroxy or C_{1-4} alkoxy;

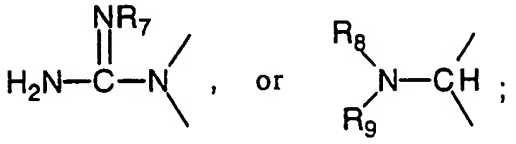
Y_2 represents N or CH, with the proviso that when Y_1 is CR_6 then Y_2 cannot represent CH;

Y_3 represents N or CH, with the proviso that when Y_2 is N then Y_3 cannot represent N;

one of Z_1 or Z_2 represents Z and the other represents CH_2, with the proviso that when Y_3 represents N, then Z_2 represents CH_2;

Z represents a group of formula:





R_7 represents hydrogen or C_{1-4} alkyl;

R_8 and R_9 independently represent hydrogen or C_{1-4} alkyl, or they can be bonded together forming a C_{2-5} polymethylene chain;

D represents carboxy or a metabolically labile ester or amide thereof;

aryl in the above definitions represents phenyl or naphthyl which can be optionally substituted with one or more groups independently selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, carboxy, cyano, nitro, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylthio or C_{1-4} alkylcarbonylamino and wherein two substituents on adjacent carbon atoms can be bonded together forming a methylenedioxy group;

heteroaryl in the above definitions represents an aromatic monocyclic 5- or 6-membered heterocycle or an aromatic bicyclic 9- or 10-membered heterocycle containing from one to four heteroatoms selected from N, O and S, and which can be optionally substituted with one or more groups independently selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, carboxy, cyano, nitro, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylthio or C_{1-4} alkylcarbonylamino;

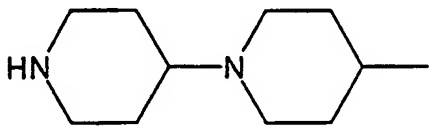
or a salt, solvate or prodrug thereof.

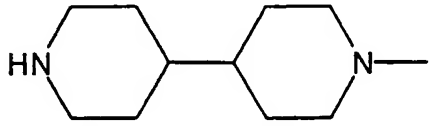
2.- A compound as claimed in claim 1 wherein X_2 represents C substituted with the group R_1.

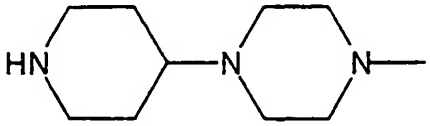
3.- A compound as claimed in claim 1 or 2 wherein X_1, X_3, X_4 and X_5 represent CR_2 or one of X_1, X_3, X_4 and X_5 represents N and the other represent CR_2.

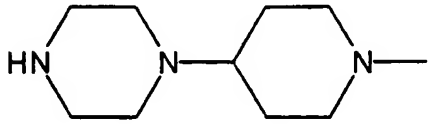
4.- A compound as claimed in any one of claims 1 to 3 wherein m represents 0.

5.- A compound as claimed in any one of claims 1 to 4 wherein R_1 represents a group selected from:

(a) 

(b) 

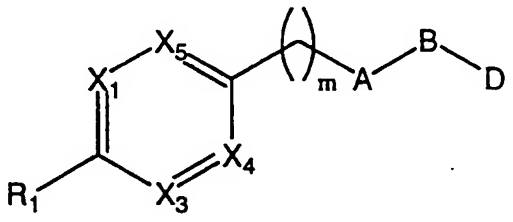
(c) 

(d) 

6.- A compound as claimed in any one of claims 1 to 5 wherein A represents $-CONR_3-$.

7.- A compound as claimed in any one of claims 1 to 6 wherein B represents ethylene which can be optionally substituted as defined in claim 1.

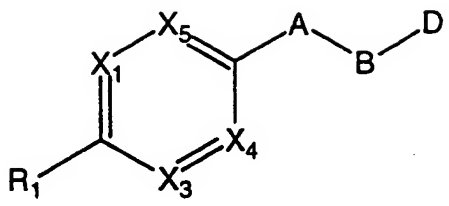
8.- A compound as claimed in claim 1 of formula Ia



Ia

wherein X_1, X_3, X_4, X_5, R_1, m, A, B and D are as defined in claim 1.

9.- A compound as claimed in claim 1 of formula Ib

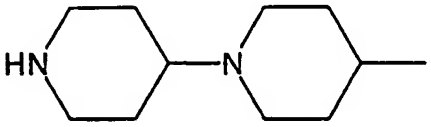


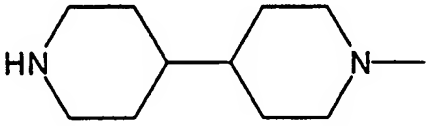
Ib

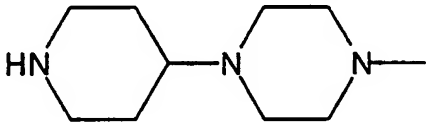
wherein X_1, X_3, X_4, X_5, R_1, A, B and D are as defined in claim 1.

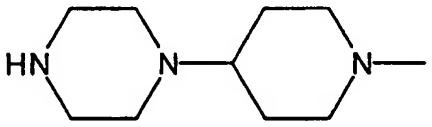
10.- A compound as claimed in claim 9 wherein X_1, X_3, X_4 and X_5 represent CR_2 or one of X_1, X_3, X_4 and X_5 represents N and the other represent CR_2.

11.- A compound as claimed in claim 10 wherein R_1 represents a group selected from:

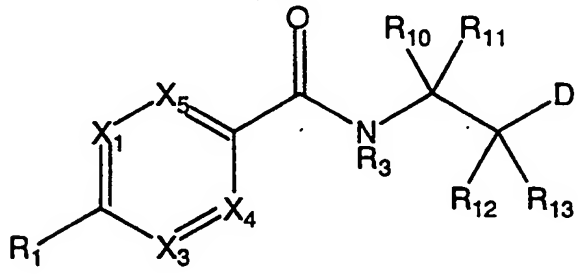
(a) 

(b) 

(c) 

(d) 

12.- A compound as claimed in claim 1 of formula Ic

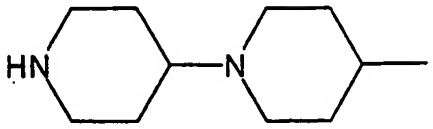


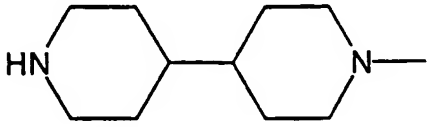
Ic

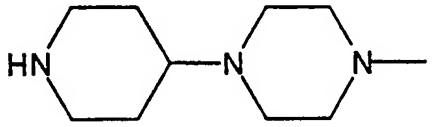
wherein:

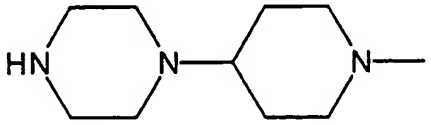
X_1, X_3, X_4 and X_5 represent CR_2 or one of X_1, X_3, X_4 and X_5 represents N and the other represent CR_2;

R_1 represents a group selected from:

(a) 

(b) 

(c) 

(d) 

;

R_{10}, R_{11}, R_{12} and R_{13} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl, arylC_{3-7} cycloalkyl, heteroarylC_{0-4} alkyl, $R_3R_4NC_{0-4}$ alkyl, $R_5SO_2NR_3C_{0-4}$ alkyl, $R_5CONR_3C_{0-4}$ alkyl, $R_5OCONR_3C_{0-4}$ alkyl, $R_3R_4NCONR_3C_{0-4}$ alkyl, $R_5SO_qC_{0-4}$ alkyl, $R_3R_4NSO_2C_{0-4}$ alkyl, $R_3R_4NCOC_{0-4}$ alkyl, R_5COC_{0-4} alkyl, $HOOCC_{0-4}$ alkyl, R_5OOCC_{0-4} alkyl, hydroxyC_{0-4} alkyl or R_5OC_{0-4} alkyl; and

R_2, R_3, R_4, R_5, q and D are as defined in claim 1.

13.- A compound as claimed in claim 12 wherein:

R_{10} and R_{11} represent hydrogen; and

one of R_{12} or R_{13} represents hydrogen and the other represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{3-7} cycloalkylC_{0-4} alkyl, arylC_{0-4} alkyl, arylC_{3-7} cycloalkyl, heteroarylC_{0-4} alkyl, $R_3R_4NC_{0-4}$ alkyl, $R_5SO_2NR_3C_{0-4}$ alkyl, $R_5CONR_3C_{0-4}$ alkyl, $R_5OCONR_3C_{0-4}$ alkyl, $R_3R_4NCONR_3C_{0-4}$ alkyl, $R_5SO_qC_{0-4}$ alkyl, $R_3R_4NSO_2C_{0-4}$ alkyl, $R_3R_4NCOC_{0-4}$ alkyl, R_5COC_{0-4} alkyl, $HOOCC_{0-4}$ alkyl, R_5OOCC_{0-4} alkyl, hydroxyC_{0-4} alkyl or R_5OC_{0-4} alkyl.

14.- A compound as claimed in claim 1 selected from:

3-[N-[4-(4,4'-bipiperidin-1-yl)benzoyl]amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(methylsulfonylamino)benzoyl]amino]-propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(propylsulfonylamino)benzoyl]amino]-propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(2-propylsulfonylamino)benzoyl]amino]-propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(butylsulfonylamino)benzoyl]amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(*tert*-butylcarbonylamino)benzoyl]amino]-propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-3-nitrobenzoyl]amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-3-(butylsulfonylamino)benzoyl]amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(methoxycarbonylamino)benzoyl]amino]-propionic acid;

3-[N-[2-(benzylsulfonylamino)-5-(4,4'-bipiperidin-1-yl)benzoyl]amino]-propionic acid;

3-[N-[2-(benzylsulfonylamino)-4-(4,4'-bipiperidin-1-yl)benzoyl]amino]-propionic acid;

4-[N-[2-(benzylsulfonylamino)-4-(4,4'-bipiperidin-1-yl)benzoyl]amino]butyric acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-[(4-methoxyphenyl)sulfonylamino]benzoyl]-amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(4-tolylsulfonylamino)benzoyl]amino]-propionic acid;

3-[N-[2-[4-(acetylamino)phenylsulfonylamino]-4-(4,4'-bipiperidin-1-yl)-benzoyl]amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-[(3-pyridylacetyl)amino]benzoyl]amino]-propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(styrylsulfonylamino)benzoyl]amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-(2-naphthylsulfonylamino)benzoyl]amino]-propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-[(1-phenyl-1-cyclopropanecarbonyl)amino]-benzoyl]amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)benzoyl]amino]-2-methylpropionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)benzoyl]amino]-3-methylpropionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)benzoyl]amino]-2(*S*)-[(2-thienylcarbonyl)amino]-propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)benzoyl]amino]-3-phenylpropionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)benzoyl]amino]-2(*S*)-(phenylsulfonylamino)-propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-trifluoromethylbenzoyl]amino]propionic acid;

3-[N-[4-(4,4'-bipiperidin-1-yl)-2-fluorobenzoyl]amino]propionic acid;

3-[N-[6-(4,4'-bipiperidin-1-yl)nicotinoyl]amino]propionic acid;

3-[N-[6-(4,4'-bipiperidin-1-yl)nicotinoyl]amino]-3-methylpropionic acid;

3-[N-[[4-(4,4'-bipiperidin-1-yl)phenyl]sulfonyl]amino]propionic acid;

3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid;

3-methyl-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid;

2-methyl-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid;

3-phenyl-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid;

3-[N-[6-[4-(4-piperidinyl)piperazin-1-yl]nicotinoyl]amino]propionic acid;

3-methyl-3-[N-[6-[4-(4-piperidinyl)piperazin-1-yl]nicotinoyl]amino]propionic acid;

3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-2-trifluoromethylbenzoyl]amino]-propionic acid;

3-[N-[2-methyl-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid;

3-[N-[[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]sulfonyl]amino]propionic acid;

3-[N-[2-chloro-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid;

3-[N-[2-fluoro-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]propionic acid;

3-phenyl-3-[N-[6-[4-(4-piperidinyl)piperazin-1-yl]nicotinoyl]amino]propionic acid;

3-[N-[2-fluoro-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-3-phenyl-propionic acid;

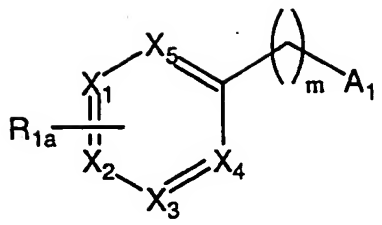
3-[N-[2-chloro-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-3-phenyl-

propionic acid;
3-[N-[2-methyl-4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-3-phenyl-propionic acid;
3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-2(*S*)-[(2-thienyl-carbonyl)amino]propionic acid;
3-[N-[2-benzylamino-4-(4,4'-bipiperidin-1-yl)benzoyl]amino]propionic acid;
1-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]piperidin-3-carboxylic acid;
2(S)-(benzyloxycarbonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-benzoyl]amino]propionic acid;
2(S)-(isovalerylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]-amino]propionic acid;
3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-2(S)-[(2-thienyl)-sulfonylamino]propionic acid;
2(S)-(phenylsulfonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]-amino]propionic acid;
2(S)-[(4-methoxybenzoyl)amino]-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-benzoyl]amino]propionic acid;
2-methyl-3-[N-[6-[4-(4-piperidinyl)piperazin-1-yl]nicotinoyl]amino]propionic acid;
3-[N-[4-[4-(piperazin-1-yl)piperidin-1-yl]benzoyl]amino]butyric acid;
3-methyl-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]butyric acid;
3-[N-[4-[4-(piperazinyl)piperidin-1-yl]benzoyl]amino]-2(S)-[(2-thienyl-carbonyl)amino]propionic acid;
3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-2-trifluoromethylbenzoyl]amino]-2(S)-[(2-thienylcarbonyl)amino]propionic acid;
2(S)-[(2-furoyl)amino]-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]-amino]propionic acid;
2(S)-[(3-furoyl)amino]-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]-amino]propionic acid;
2(S)-(n-butoxycarbonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-2-trifluoromethylbenzoyl]amino]propionic acid;
2(S)-(n-butoxycarbonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-

benzoyl]amino]propionic acid;
2(S)-(n-butoxycarbonylamino)-3-[N-[4-[4-(piperazin-1-yl)piperidin-1-yl]-benzoyl]amino]propionic acid;
N-[2-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]acetyl]-L-leucine;
N-[2-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]acetyl]-L-tyrosine;
N-[2-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]acetyl]-L-phenylalanine;
N-methyl-N-[2-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]acetyl]glycine;
N-[2-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]acetyl]-D-phenylalanine;
2(S)-(benzylsulfonylamino)-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]-amino]propionic acid;
2(S)-(benzyloxycarbonylamino)-3-[[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-phenyl]amino]carbonyl]propionic acid;
2(S)-[3-(4-fluorophenyl)ureido]-3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]-benzoyl]amino]propionic acid;
2(S)-(benzylsulfonylamino)-3-[N-[4-[4-(piperazinyl)piperidin-1-yl]benzoyl]-amino]propionic acid;
2(S)-[(4-methoxyphenyl)sulfonylamino]-3-[N-[4-[4-(piperazinyl)piperidin-1-yl]benzoyl]amino]propionic acid;
3-[N-[4-[4-(4-piperidinyl)piperazin-1-yl]benzoyl]amino]-2(S)-[2-(2-thienyl)-acetylamino]propionic acid;
2-[2-oxo-3-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]imidazolidin-1-yl]acetic acid;
N-benzyl-N-[[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]acetyl]glycine;
2(S)-(phenylsulfonylamino)-3-[[N-[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]-amino]carbonyl]propionic acid;
2-[[[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]amino]carbonyloxy]acetic acid;
N-benzyl-N-[[4-[4-(4-piperidinyl)piperazin-1-yl]phenyl]aminocarbonyl]glycine;
or a salt, solvate or prodrug thereof.

15.- A process for preparing a compound of formula I as defined in claim 1 which comprises:

(a) reacting a compound of formula (II)

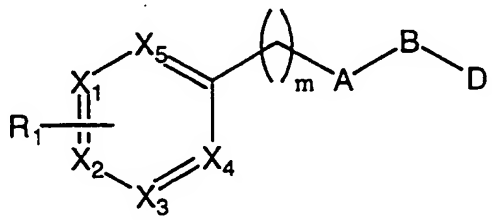


II

with a compound of formula A_2-B-D (III),

wherein B, D, m, X_1, X_2, X_3, X_4 and X_5 are as defined in claim 1, R_{1a} represents a group R_1 as defined in claim 1 or a group convertible thereto, and one of A_1 or A_2 represents -COOH (or a reactive derivative thereof), $-SO_2Cl$ or -NCO and the other represents $-NHR_3$ or one of A_1 or A_2 represents -NCO and the other represents -OH, followed when necessary by the conversion of a group R_{1a} into a group R_1 and/or the removal of any protecting group that may be present; or

(b) deprotecting a compound of formula I'



I'

wherein A, B, D, m, R_1, X_1, X_2, X_3, X_4 and X_5 are as defined in claim 1 but at least one of them contains a protecting group; or

(c) converting, in one or a plurality of steps, a compound of formula I into another compound of formula I; or

(d) converting a compound of formula I wherein D represents a carboxy group into a metabolically labile ester or amide thereof; and

(e) if desired, after the above steps, treating a compound of formula I with an acid or a base to give the corresponding addition salt.

16.- A pharmaceutical composition which comprises an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable

salt, solvate or prodrug thereof in admixture with one or more pharmaceutically acceptable excipients.

17.- The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for the treatment or prevention of GPIIb/IIIa-mediated disorders.

18.- The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for inhibiting platelet aggregation.

19.- The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for inhibiting the binding of fibrinogen to its receptor.

20.- The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for the treatment or prevention of thromboembolic disorders.

21.- A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof in combination with one or more therapeutic agents and one or more pharmaceutically acceptable excipients.

22.- A pharmaceutical composition as claimed in claim 20 wherein the therapeutic agent is selected from a platelet aggregation inhibitor, a thrombolytic agent or an anticoagulant agent.